R&D innovative technologies in the pharmaceutical sector and the challenges in their implementation in the EU

By

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STUDENT DECLARATION

I hereby confirm that this dissertation titled "R&D innovative technologies in the pharmaceutical sector and the challenges in their implementation in the EU", which is presented in partial fulfilment of the requirements for the award of the MSc in Pharmaceutical Business and Technology, represents my original work, under the supervision of Dr. Cecilia Vasquez-Robinet.

I have appropriately indicated all sources used in the preparation of this study through accurate referencing. I also verify that I have neither copied nor plagiarised the work of anyone else.

To be filled by the Student: To be filled by the Supervisor:

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“You are truly an explorer”

Martinus Veltman

ABSTRACT

The pharmaceutical industry is constantly changing, and patients necessities waiting for treatment are numerous. New diseases and those that do not have treatment are constant factors demanding the pharmaceutical industry look at recent trends in R&D, search for different scientific solutions, and focus on innovation.

It is essential to know the R&D innovative technologies, applications, and development in the current landscape, driving the pharmaceutical sector forward. In the new context, where the European Union has 27 countries, the European Medicines Agency (EMA) regulates approvals and population worldwide lives in the context of the Covid-19 pandemic. The vision of opting for new technology, knowing the trends in R&D, science, and innovation opens a panorama of opportunities and challenges for the pharmaceutical sector. The study comprises qualitative and quantitative approaches to investigated innovative technologies and their challenges in pharmaceutical R&D. Data generation have been carried out with scientists working in R&D, pharmaceutical professionals, and regulatory professionals, followed by an analysis of information available through documentary research. Findings have shown that the most challenging factor influencing the R&D innovative technology approval is regulatory standardization. This factor has led to the major constraint in implementing innovative technologies, while Technology cost has been identified as the second challenging constraint. R&D innovative technologies represent an advantage in a COVID-19 pandemic context through gene therapies and digital transformation with access to big data in real-time. R&D management performs a principal role in the implementation of new technology. As Claud-based data management has been the main Pharma 4.0 element implemented in the EU in recent years, Policy and regulatory activity and Data integrity and cybersecurity will represent the pharmaceutical sector's major challenges in the next ten years.

Key words: Research and Development, Pharmaceutical Industry, Innovation, R&D management, Pharma 4.0, Gene therapies, Artificial Intelligence.

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ABBREVIATIONS

AAVs	Adeno-associated viruses
Ads	Adenoviruses
AdvDip	Advanced Diploma
AI	Artificial Intelligence
AQbD	Analytical Quality-by-Design
ATMPs	Advanced Therapy Medical Products support
ATP	Analytical Target Profile
BA	Bachelor Degree
CAAs	Critical Analytical Attributes
CAR-T	Chimeric antigen receptor T
COVID-19	Coronavirus disease
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CRISPRa	Clustered Regularly Interspaced Short Palindromic Repeats Activator
CRISPRi	Clustered Regularly Interspaced Short Palindromic Repeats Interference
DNA	Deoxyribonucleic Acid
DoE	Design of experiments
DTIF	Disruptive Technology and Innovation Fund
EMA	European Medicines Agency
EU	European Union
FDA	(US) Food and Drug Administration
HIV	Human Immunodeficiency virus
HTVS	Hight Throuput Virtual Screening
LBVS	Ligand-Based Virtual Screening
MIT	Technology Innovation Management
mRNA	Messenger RNA
MS	Master Degree
NDA	New Drug Approvals
PAT	Process Analytical Technology
PDB	Protein Data Bank
PhD	Doctor of Philosophy
QRM	Quality Risk Management
QSAR	Quantitative Structure-Activity Relationship
R&D	Research and Development
RNA	Ribonucleic Acid
SAR-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SBVS	Structure-Based Virtual Screening
VLAIO	Agency for Innovation and Entrepreneurship
ZFNs	Zinc-Finger nucleases

CHAPTER I

INTRODUCTION

1.1 Background of the study

One of the main topics to be investigated in the pharmaceutical sciences is drug research and development in the pharmaceutical sector. The R&D term has been widely linked to innovation. It includes all activities to introduce a high-quality new product to the market and stay ahead in the area. However, during this process, the most attrition rate occurs in the early clinical stages. A pipeline has more probability of reaching the market when it survives phase II.

The R&D is essential to stay competitive and follow the rapid rate of technological advancement allow pharmaceutical companies to create new patents and bring new therapies to the patients.

According to the index of innovation and invention 2021, in an analysis of the top thirty pharmaceutical companies worldwide considering the expenses in the process of bringing a new drug to the market, the average R&D cost per approval in five years is US$4,815 million (IDEA Pharma, 2021). The industry-funded Tufts Center for Drug Development reports that the cost of a new therapy until makes it to the market is US$2.6 billion, and the Neglected Diseases Initiative (DNDi) estimated £100-150 million per chemical entity (Annett, 2021).

1.2 Statement of the problem

The increasing cost of a new chemical entity represents a constant concern for the pharmaceutical industry. In the attempt to discover new therapies to improve patients health, the development of a new drug has resulted in high drug prices. According to the World Bank, this has greatly affected beyond the expected, since 100 million people are pushed into poverty as they would prefer to buy medicines to treat a disease over other necessities. Worldwide, the number of people who cannot access medications is 2 billion, representing an economic impact because ill people cannot work (Annett, 2021).

In the current pharmaceutical landscape, the European Union (EU) has adopted a new pharmaceutical strategy due to the global pandemic, creating a future-proof regulatory framework and supporting research and technology in the industry to meet therapeutic needs (Draguet, 2020).

The European Union has invested in innovation to achieve future stability, trying to be at the technological forefront. According to the European Innovation Scoreboard 2021, Horizon Europe, the world's leading research and innovation program, has supported innovation with a budget of € 95.5 billion for 2021-2027, including the R&D expenditures in the public sector and the private sector (EURAXESS, 2021). The European pharmaceutical industry is the second-largest market in the world. According to the Pharma strategy report, it provides 800,000 jobs and a €109.4 billion revenue. Furthermore, the EU pharmaceutical strategy tries to improve the current system based on four pillars: to address unmet medical needs, preventing before the crisis, supporting innovation and sustainability, and ensuring a strong EU voice globally through safety and quality standards. However, a new approach is needed to drive technological advances to ensure digital transformation through artificial intelligence and a well-performing pharmaceutical market, including the entire lifecycle and the adoption of innovative technologies (Draguet, 2020). Therefore, to achieve it is important to be aware of the challenges those new technologies have to face in their implementation.

1.3 Purpose of the study

The purpose of this study is to evaluate the principal trends in R&D, science and innovation in the pharmaceutical sector and their current challenges in the EU, considering the recent landscape and the perspectives of pharmaceutical and biopharmaceutical professionals. The analysis pretends to lay out the challenges for new technologies such as Gene therapy and Pharma 4.0 in the R&D area.

1.4 Hypothesis

Challenges are limiting the application of innovative trends in pharmaceutical R&D in the EU, such as Gene therapies and Pharma 4.0, due to the absence of knowledge, lack of regulation and high cost of its applicability.

1.5 Research objectives

General Objective

Identification of the main trends in R&D, science and innovation in the pharmaceutical sector and the challenges they are facing in the current EU landscape.

Specific Objectives

Objective 1. Identification of the principal trends in R&D, science and innovation in the EU pharmaceutical sector.

Objective 2. Analysis of the R&D innovative practices and their main challenges in the current landscape.

Objective 3. Evaluation of the potential of innovative R&D technologies in the COVID-19 pandemic context.

1.6 Research questions

What are the main trends in R&D, science and innovation in the pharmaceutical sector in the current EU landscape?

Which challenges are facing those trends in the current EU landscape?

What is the potential of new R&D technologies in the COVID-19 pandemic context?

1.7 Scope and limitation of the study

This study covers the main trends in R&D, science and innovation in the pharmaceutical sector to research the challenges they face in the current EU landscape from different perspectives of scientists, regulatory professionals and pharmaceutical professionals. The scope of this study does not cover each pharmaceutical company-specific process in the innovative technologies application.

1.8 Outline of the dissertation

This research about R&D innovative technologies is structured following the quantitative approach through a well-structured questionnaire. The dissertation has tried to give an overview of the study significance, following a scientific approach, analysing the topic, and providing a conclusion through six chapters.

Chapter I covers the introduction describing the main research idea, the background of the study, the importance of the research topic, and the central objectives of the analysis supporting the hypothesis.

Chapter II provides an overview with a critical understanding of the literature available. It has tried to present the context of the R&D in the pharmaceutical sector, the important role of innovation in developing new products, a brief introduction of recent trends such as Gene and cell therapies, focusing on the most remarkable achievements in the field, CRISPR and CAR-T cells. It is followed by the analytical review of the fourth industrial revolution, Pharma 4.0, summarising the advantages of implementing artificial intelligence tools to drug discovery, the foundation of the digitalization era, and the use of PAT and AQbD systems in the R&D. The literature review chapter summarises the R&D management role and those trends potential in the COVID-19 context.

Chapter III addresses the main research philosophy approaches and the methodology choices that have followed. It describes the strategy of the study and the population where the study has been conducted.

Chapter IV describes de results obtained from the research. The data are analysed through statistical tools and have been explained graphically.

Chapter V is a critical discussion of the results, comparing the literature and supporting the data by the scientific facts.

Chapter VI presents the conclusions and recommendations from the research, analysis discussion, and further implications.

1.9 Significance of the study

Identifying the challenges in implementing emergent innovative technologies in the pharmaceutical business is highly advantageous, Not only does it provide a competitive advantage, but it also helps in evaluating the future of its application in the current EU landscape. One of the major bottlenecks in the pharmaceutical industry is during the research and development process of new medicine. The research, the work of many scientists and industry professionals, moves day by day, trying to find innovative technologies at a lower cost and, most importantly, to provide an early solution to the patient waiting for treatment. It is essential to know the affordability of these technologies, and this study can provide that information.

CHAPTER II

LITERATURE REVIEW

2.1 Overview.

Innovation in pharmaceutical research and development represents a critical issue. For many years, the R&D process from the drug discovery stage to the bringing of new drugs to the market has resulted in a high cost because of low productivity and lack of return on investment. Notwithstanding the diversity of drug targets, safety and treatment efficacy requires following the same process to get approval by the regulatory entities (Romasanta et al., 2020).

In the earliest stages, target identification and the action mechanisms elucidation require the design of a lead compound. Once the scientists identify the lead compound, the efficacy and safety are tested in cells and animals. After drug discovery and drug development stages, the drug enters clinical trials in humans. Phase I consists of the dose-ranging on healthy volunteers to evaluate toxicity. Phase II embraces drug testing on participants to assess efficacy and safety. Subsequently, to establish possible side effects and drug safety, the drug is tested in a large population in Phase III. Finally, Phase IV studies look at medicines the regulatory entity has already approved, ensuring the drug reaches its patients guaranteeing pharmacovigilance (Figure 2.1) (Romasanta et al., 2020).
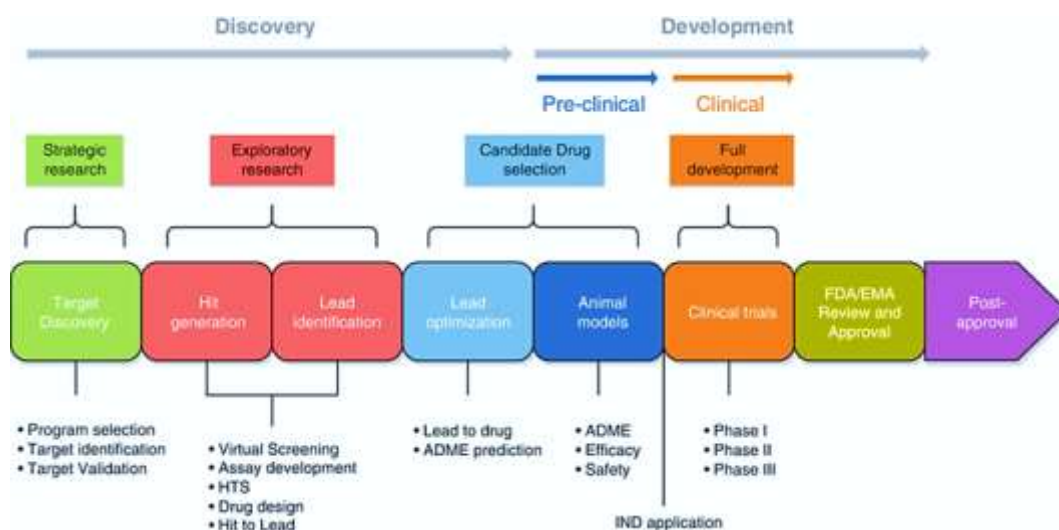
Figure 2. 1 Drug Discovery and Development process (Duelen et al., 2019).

In the process of bringing these new drugs to the market, further research to uncover biological mechanisms by universities and public research institutes lacks a clear path towards commercialization and makes it unappealing for the industry. However, increasing research collaborations in recent years have improved drug discovery, leading many pharmaceutical companies to look towards the exploration of innovative technologies in R&D (Romasanta et al., 2020).

Public money plays an essential role in this process because they pay one and two-thirds of the R&D cost. Some of those fundings are confidential, and price agreements between national governments and the clouds R&D costs are unavailable. Further collaboration seems necessary, where the public funding could stipulate open data repositories from basic research to improve science. The human genome project is an example of it (Annett, 2021).

Prior research suggests that pharmaceutical companies have treated diseases for years through improving research and bringing patients safe medication. However, while conventional therapies have treated the symptoms and increased life expectancy, they rarely cure. In that scenario, new technologies such as gene and cell therapies might be an opportunity to explore and implement (Hosseini et al., 2021). The healthcare sector is looking for innovation to bring new alternatives for the patients, developing novel therapeutic modalities and rethinking the technologies applying in the drug discovery and development process, manufacturing, regulatory cooperation, and pricing strategy. However, the pharmaceutical industry incorporates a novel technology until it is mature and its application does not represent a risk for patient safety (Melchner von Dydiowa et al., 2021).

In this purpose to preserve patient safety, the high cost and time involved in drug development, the slow communication and the lack of faster access to track the R&D process are opening a door for the digitalization era. Some tools, such as Pharma 4.0, is changing the pharmaceutical sector as we know it (Aceto et al., 2020). 2020 was a clear example of changing when the COVID-19 pandemic came to test the existing system and underline how the research and development process has to move to innovative technologies (Aceto et al., 2020; Khan and Basak, 2021).

2.2 Gene and Cell therapy

Gene therapy is a developing technology offering different solutions to genetic diseases. It involves correcting defective genes in cells of an individual, using a set of techniques to prevent or cure monogenic, multigenic and infectious diseases. Essentially, there are two kinds of gene therapy; gene augmentation and gene editing (Figure 2.2).
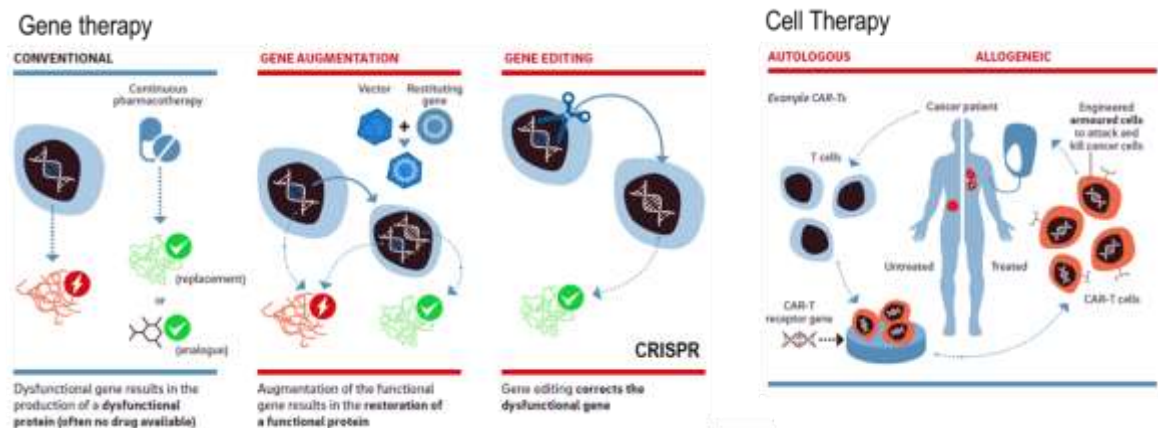
Figure 2. 2 Gene therapy (gene augmentation and gene editing), and cell therapy (autologous and allogenic). Modified from (Hosseini et al., 2021).

In the first case, a piece of DNA is introduced into the cell nucleus through an adenovirus to ensure the new DNA arrives in the objective and restore the functional protein, viral or non-viral vectors are used to introduce the therapeutic gene in the cells (Hosseini et al., 2021). A vector is a vehicle that transports the therapeutic gene and other necessary elements into the affected cells. Viral vector-based gene therapy is achieved by in vivo delivering the therapeutic gene into the patient by vectors based on retroviruses, adenoviruses (Ads) or adeno-associated viruses (AAVs) (Ekstedt et al., 2021). The second type of gene therapy, is applied by modifying deletions and correcting the existing DNA using gene scissors to fix the dysfunctional gene, it can be *ex-vivo* or *in-vivo* (Figure 2.3) (Hosseini et al., 2021).

A therapeutic transgene can be delivered *ex vivo*, whereby the patient cells are extracted and cultured outside of the body. Cells are then genetically modified by introducing a therapeutic transgene and then are reintroduced back into the patient (Bulcha et al., 2021). It is the case of Cell therapy, where the cells can be extracted from the patient themselves, called Autologous or from different patients, allogeneic cell therapy (Hosseini et al., 2021).
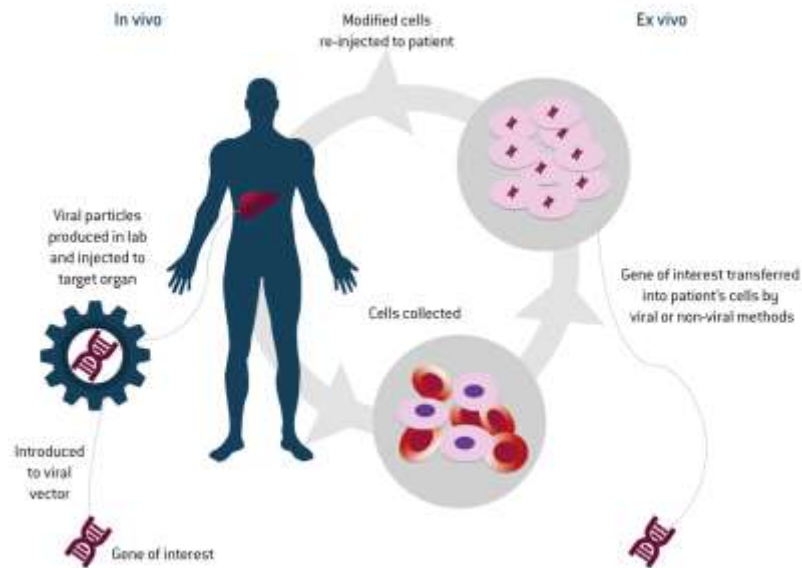
Figure 2. 3 Gene therapies (Lonza, 2021).

Gene and cell therapies represent potential blockbusters in Pharma. Six pharmaceutical companies are using already those platforms, and most of them are in phase II of clinical trials. The study of Hoseeini et al. (2021) showed that the forecast progression for Gene and Cell therapies sales would reach EUR 17.2 and EUR 10.7, respectively, in 2026 (Figure 2.4) (Hosseini et al., 2021).

CELL AND GENE THERAPY POTENTIAL BLOCKBUSTERS

	Company	Platform	Indication	Phase	Sales 2026e
Zolgensma	Novartis	AAV	SMA	Marketed	EUR 1.6 bn
MultiStem	Athersys	Stem cell	Various	Phase III	EUR 1.3 bn
Zynteglo	bluebird bio	LV	Beta thalassemia	Marketed	EUR 1.2 bn
LN-144	Iovance	TILs	Melanoma	Phase II	EUR 1.1 bn
CTX001	CRISPR Tx	CRISPR	Beta thalassemia	Phase II	EUR 1.1 bn
LN-145	Iovance	TILs	Solid tumors	Phase II	EUR 0.8 bn
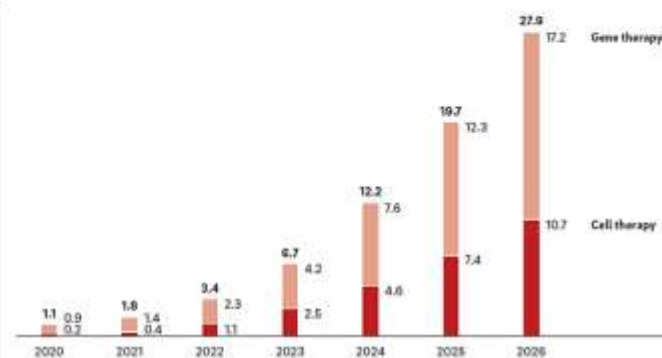
Figure 2. 4 Gene and Cell therapy potential blockbusters. Modified from(Hosseini et al., 2021).

2.2.1 CRISPR

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a new technology, and the most well-known example of genetic editing or genome engineering to modify organisms DNA. As a genetic tool, it provides development as a base editor, prime editor, epigenetic editor, and CRISPR interference (CRISPRi) and CRISPR activator (CRISPRa) gene regulators. It has three foundational genome editing technologies: CRISPR/Cas, Transcription activator as effector nucleases and Zinc-Finger nucleases (ZFNs) (LI et al., 2021).

CRISPR/Cas9 gene-editing technique relies on a complex immune system in bacteria protecting them against viruses. It is an acquired or adaptive immunity that "remembers" the DNA sequences of pathogens from previous attacks and cuts their DNA in a new infection event. This combination of recognition and cutting in the simplest variant, RNA encoding a protein called Cas9 and a recognition sequence are injected into the cell. The cell uses RNA to synthesize the protein, which is then put to work together with the added recognition RNA: Cas9 cuts the double-stranded DNA exactly where the associated RNA fragment tells it to do it. Since CRISPR/Cas9 gene-editing technique can synthesize any RNA sequence artificially, such a combination allows cutting any genome anywhere (Figure 2.5) (LI et al., 2021).
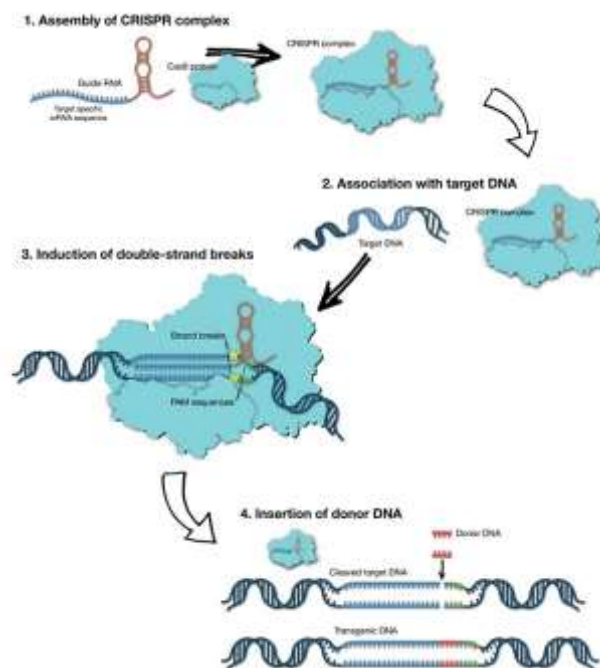
Figure 2. 5 Mechanism of CRISPR/Cas9 genome editing (Costa et al., 2017).

CRISPR/Cas9 system has high growth potential. Its capability to edit cells (either human, animal or plant) to correct genetic level mutations and its applications in basic research turns to CRISPR/ Cas9 highly usable in all biotechnological settings. Its uses involve tackling fundament issues from human and animal biology, somatic applications and reproductive applications feasibility, holding great promise for the future of medical science. Some of the diseases where this technology is being applied include cancer, discovering the role of genomic mutations in carcinogenesis, spinal muscular atrophy, and HIV through the alteration of CD4 T lymphocytes (Zaami et al., 2021).

CRISPR has been showing potential to treat viral diseases such as HIV and is currently an alternative for SARS-CoV-2. The expectations for this innovative technology giving a benefit increase at the same time that the concerns about it do. Ethical implications, safety, risk and the need for regulation of this technology have mainly been discussed since a Chinese scientist attempted to make a human preimplantation embryo resistant to HIV infection, dismissing the ethical issues. Besides, other research used treated stem cells to acute lymphocytic leukaemia and HIV showing severe side effects promptly. Those circumstances make editing tools quite unpredictable, and extreme caution is advisable in its use. However, the concerns do not overshadow the advantages and opportunities that they represent for human health (Zaami et al., 2021).

2.2.2 CAR-T cell therapy

One of those developments have been the CAR-T cells, representing one of the most remarkable breakthroughs in cancer medicine (Safarzadeh Kozani et al., 2021). CAR-T therapy in the treatment of B-cell acute leukaemia and lymphoma has given life span to cancer patients. However, it has faced several side effects such as neurotoxicity, cytokine release syndrome and graft rejection, besides efficacy shortcomings (Safarzadeh Kozani et al., 2021).

Modified cells include receptors (CAR) capable of detecting and killing carcinogenic cells. In this stage, patients may suffer several adverse effects because it is subject to body acceptance. As a result, a considerable amount of resources and personnel training to execute its application are necessary. The observable challenge for the Pharma sector and regulatory entities is the in-depth understanding of the benefits and adverse effects patients face. Looking for more high-quality data on this treatment to track CAR-T cell

receptors in patients once treatment has started could be achieved by strengthening the EudraVigilance System (Association (EHA), 2021; Holstein and Lunning, 2020).

2.3 Pharma 4.0 in the pharmaceutical R&D

Pharma 4.0 is an emerging trend looking forward to evolution in the pharmaceutical sector providing digital solutions. Its technologies consider four dimensions: Smart Manufacturing, Smart Products, Smart Supply Chain and Smart Working. The base of these technologies is the internet source, cloud services, big data and analytics (ISPE, 2021; Reinhardt et al., 2020).

Pharma 4.0 can improve the pharmaceutical R&D process in the current landscape of developing a new drug and the patented time frame through artificial intelligence. Those tools can provide personalised and precision medicine; and accompanied with apps that can help patients to monitor parameters. Currently, companies are moving to augmented reality showing a projected rate of 74% between 2018 and 2025, according to the report of Reinhardt and collaborators. In the path to increase Quality and time optimisation in the development of drug products (Reinhardt et al., 2020), Pharma 4.0 is focusing on starting materials, avoid lack of manufacturing process automatization, improve control and more understanding of product parameters through the application of Analytical Quality-by-Design (AQbD) (Nayak et al., 2021). Alternatively, the Process Analytical Technology (PAT) gives analytical tools applied during the development and scale-up of drug substances, in-situ analysis and modelling. Consequently, the access in real-time to big data can describe systematic structure related activities that are whiting the entire product development lifecycle improving its process (Reinhardt et al., 2020).

2.3.1 Artificial Intelligence in Drug discovery

Artificial intelligence (AI) performs an essential role in the R&D process at the drug discovery stage (Figure 2.6). Access to big data generation and storage allows scientific professionals to predict drug delivery effectiveness, physicochemical properties, bioactivity, and deduction of protein-protein interactions in hit compound research, a compound with a potential effect on treating disease. In the research field, time is valuable, and time-cutting given by AI application means optimization. There are different ways to find a hit. One of them is lead identification based on the disease identity and then the primary selection by virtual screening or De-Novo designing. Lead optimization can focus on library design, and a second screening is by computational

Biology. These tools help R&D to optimized time and continue to the phase of pre-clinical Trials and clinical development in less time than the normal process. The main tools used are Docking, Ligand-Based Virtual Screening (LBVS), Structure-Based Virtual Screening (SBVS) and QSAR. Once the lead compounds are selected, scientist can do the *In-Vitro* and *In-Vivo* bioassays (Figure 2.7) (Gupta et al., 2021).

Figure 2. 6 Artificial intelligence in health care and the pharmaceutical industry (Gupta et al., 2021).
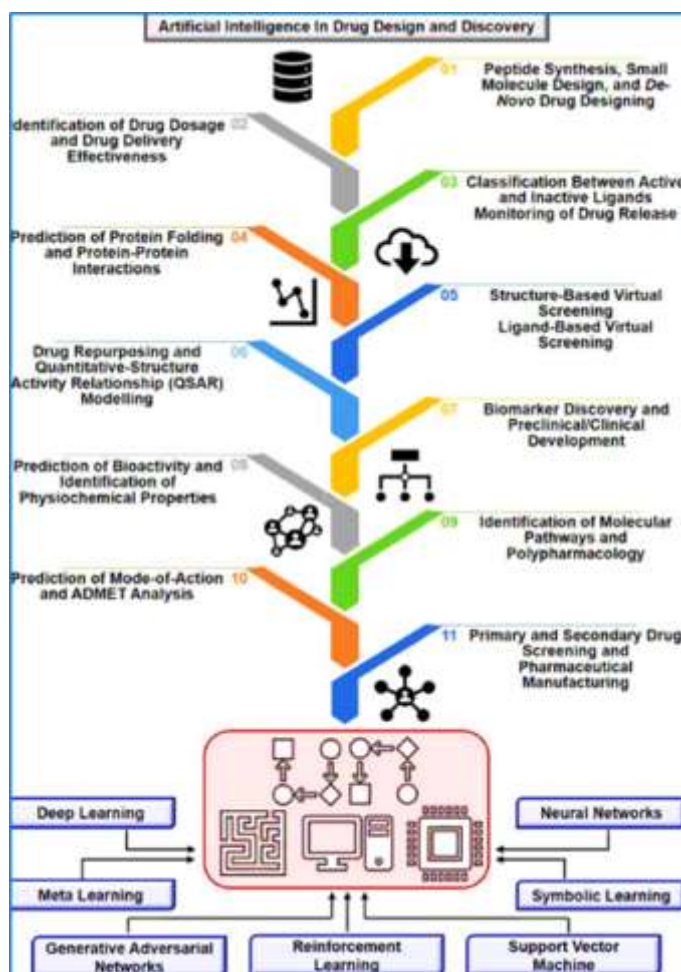
Figure 2. 7 Artificial intelligence in drug design and discovery (Gupta et al., 2021).

Artificial Intelligence as an innovation tool helps the Research and Development process saves time and materials used during the experimentation period, and increase the probability of finding a compound to treat the disease in the study (Zhu, 2020).

Big Data applications to the drug discovery stage are being used in drug repurposing. This method allows large digital libraries of compounds to assess an approved drug to treat a new disease. It enables a faster drug development process and increases the chance of being approved because the potential side effects and the ADME system are already acknowledged (Kropiwnicki et al., 2021).

The best-known tool in this field is the Hight Throughput Virtual Screening (HTVS), allowing the researcher to explore and do a compounds filtration from millions of molecules by target affinity. Repositioning is trying to extend life patents, offering new therapies at a shorter time and lower cost. To date, there are chemical, pharmacological and genetic sources. The repositioning success rate is from 30% to 75%, showing that the highest probability occurs when the drug is tested to treat a disease in the same therapeutic area (Dotolo et al., 2021).

2.3.2 Analytical Quality-by-Design

Analytical Quality-by-Design emerges as a systematic tool to guarantee the efficacy and safety of the product building the quality in the process rather than periodical inspection and testing. It can predict the real-time impact of high-risk variables on product attributes before product development, attaining stability and metabolites in biological samples. The system follows the philosophy of "right from the first step" to achieve robustness and customer satisfaction. It saves time, cost and effort (Beg et al., 2021).

The analytical Quality-by-Design involves five fundamentals steps.

Step one: establishment of the Analytical Target Profile (ATP). It constitutes to define the method objectives, design and development activities for drug products.

Step two: identification of Critical Analytical Attributes (CAAs). It is conducted by the risk assessment, which includes risk identification, risk analysis and risk evaluation. Risk analysis is usually performed employing Quality Risk Management (QRM)

Step three: design method development and analysis. One of the tools well employed in research and development is the Design of experiments (DoE). It facilitates understanding

method parameters and variables, helping to map the responses based on the studied objectives.

Step four: establishment of the method control strategy operable design region. It has to define a proven acceptable range, where the quality of the product is guaranteed.

Step five: control strategy and continuous improvement. Control strategy should be applying during all the critical stages of the method development life-cycle (Beg et al., 2021).

2.3.3 Process Analytical Technology

Process Analytical Technology (PAT) is another system to design, analyse, and control pharmaceutical processes, reducing waste and decreasing variability. Even though the rigid regulatory system sometimes is quite hesitant to introduce an innovative system because of the uncertainty, the FDA created it to helps the industry to provide biological, physical and chemical attributes to the product. The PAT aims is to support innovation and efficacy in pharmaceutical development, quality assurance and manufacturing. The PAT tools include the data acquisition and design, process analysers, process control tools and continuous improvement and management (Clegg, 2020).

There are seven steps to implement PAT:

Step one; process mapping.

Step two; Critical Quality Attributes (CQA) identification.

Step three; Experiment Design (DoE) perform and determination of the Critical Process Parameters (CPP).

Step four; Quality Risk Management (QRM) performance.

Step five; PAT identification of analysers to monitor CQA.

Step six; Development of the control strategy.

Step seven; Process Validation (Clegg, 2020).

In the Development sequence, through discovery, development and manufacturing PAT system supports four drivers (Figure 2.8). Firstly, the evaluation of the process is applicable when any new path is followed in the research phase. Risk reduction and effectiveness improvement take place in the development phase. A clear example is a risk

related to a new reaction mechanism uncertainty and the efficiency related to its time and raw material optimization. Finally, the fourth driver is the product released during the manufacturing phase to endorse identity and the parametric and real-time release testing (Clegg, 2020; Reinhardt et al., 2020).
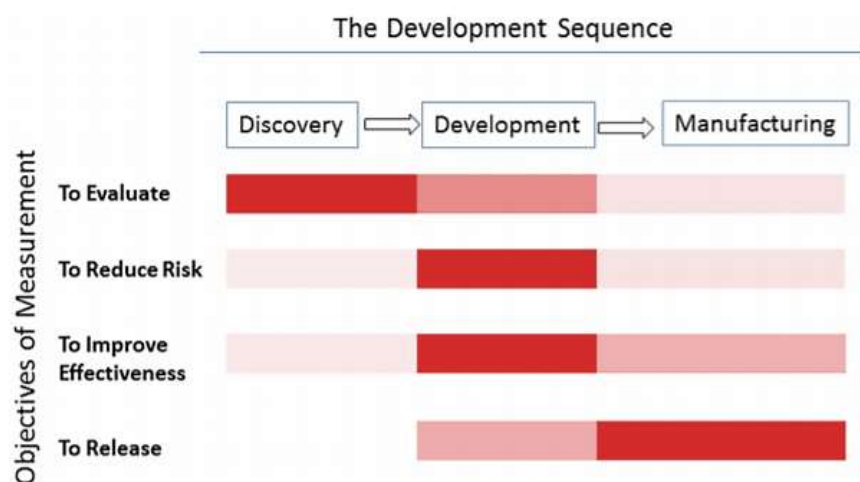
Figure 2. 8 PAT strategy objectives and the development phase (Clegg, 2020).

2.4 The role of management in R&D

The pharmaceutical industry is facing rapid changes in the attempt to commercialise a new product from drug discovery to the approved product. In this context of science innovation, management systems change dramatically to improve decision making and data value creation. The companies have applied for years of R&D management to create new products due to their high complexity and the cross-functional activities that need to be organised. The pharma sector needs to hire well-prepared people to have the right talent in the specific areas and work together as a team. Management requires the full attention of a multidisciplinary background manager to complete the individual components to make innovative products (Schweizer et al., 2020).

2.4.1 Technology Innovation Management (TIM)

Contemporary management associates the technological factor with the administrative system and the structure of the organisation. A new organisational unit now appears in the internal form of corporations, Technology Innovation Management (TIM) (Tschirky et al., 2020).

In internal technology management, most of the primary inputs for its development consist of technical and scientific knowledge. However, other information from the commercial, financial and administrative areas are also actively involved in the different stages of production, utilisation and marketing of technology packages. As an essential basis, sources providing information on the market, competition, advertising, legislation, financing, and new trends must also be included. This need establishes as a fundamental element the development of fluid communication between technological research and departments that conform the company to make the most of the investigation results and act as sources of new projects. They also are close to the top management to guarantee a global attitude concerning the company. These situations arise because of the inherent complexity of developing technological ideas and then commercialising them, which implies multidisciplinary integration between various company departments (Muegge et al., 2021).

Innovative technology affects the organisation members in various ways. It is a crucial factor to determine the tasks required and the degree of specialisation. It often defines the size and composition of the immediate workgroup and the scope for contacts with other workers and supervisors. It also affects the various functions and positions within the company and influences the specific job design of each employee. The organisation must work in a multi-faceted analysis that simultaneously deals with particular fields of the company. Therefore, in identifying variables for effective organisational operation, technology must be considered a functional, conceptual, option and decision element, and related as a vital element for both managers and scientists (Muegge et al., 2021) .

The Pharmaceutical Invention Index 2021 evaluated the thirty top Pharma companies, analysing their pipelines, the novel trials investigating, their research and development investments and the key events involved in the novel agents. Most of the pharmaceutical top innovative companies were from The US, such as Seagen, Incyte, Regeneron and Eli Lilly (the company leading the top ten). In comparing innovation in 2020 and 2021, GlaxoSmithKline (from The UK) and Sanofi (from France) increased their innovation index, while the Swiss companies Novartis and Roche and the American companies Pfizer and Gilead sciences dropped positions in the Index. The report showed US$4,815 are spent per approval in the R&D process based on the analysis of the thirty lead innovative companies (Figure 2.9) (IDEA Pharma, 2021).

2021	COMPANIES	2020
1	Eli Lilly	4
2	Roche	-1
3	Regeneron	7
4	Seagen	New
5	Incyte	New
6	GlaxoSmithKline	5
7	Sanofi	10
8	AstraZeneca	1
9	Pfizer	7
10	Gilead Sciences	5
10	Novartis	-7
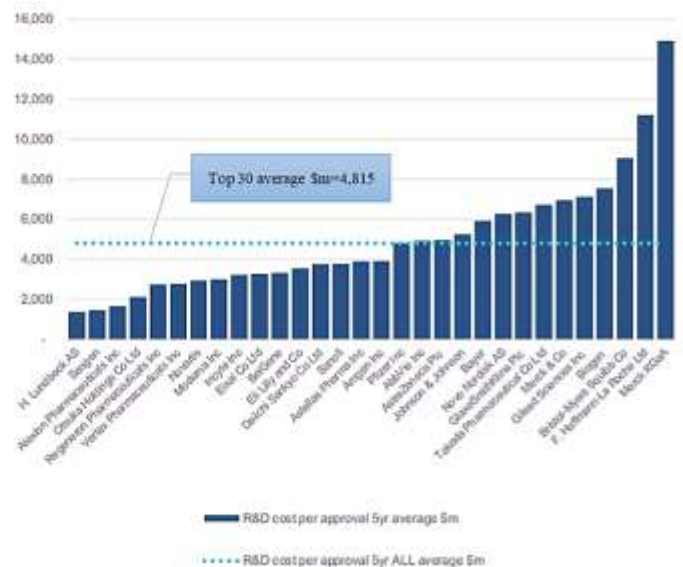
Figure 2. 9 Top Pharma and 5 year average R&D spend per approval 2015-2020 (IDEA Pharma, 2021).

The correlation between innovation and company competitiveness in its current environment brings technological capabilities at a top management level. It implies an upper management level well prepared represented by senior executives and the board of directors, where management decision-making and the knowledge of technology play a principal part in the company performance (Tschirky et al., 2020).

According to the European Innovation Scoreboard 2021, the EU has increased by 12.5% since 2014. The EU is achieving better innovation than its competitors like China, Brazil, South Africa, Russia, and India in the global landscape. However, at the same time, the United States and Japan have a performance lead over, and South Korea shows 21% above the EU was the most innovative country (Figure 2.10) (EURAXESS, 2021).

Figure 2. 10 European Innovation Scoreboard 2021 (EURAXESS, 2021).

The role of MIT in the identification and implementation strategies of tech options could improve the innovation process and increase EU companies competitiveness.

2.5 The potential of innovative technologies in the Covid-19 pandemic

The COVID-19 pandemic was a clear example highlight the necessity of driving innovation, the R&D area for years has been the change motor of the pharmaceutical industry. However, in 2019 the high-speed virus spread made scientists, health care, and pharmaceutical professionals quickly worked on virus diagnostics, treatments, and vaccines. Base on this experience, it suggests that scaled up innovation may require a better understanding of the investment and implied technology (Agarwal and Gaulé, 2021a).

In vaccine development, pharmaceutical companies followed two different technology platforms. Some of them used the viral vector vaccine, a recombinant attenuated or inactivated virus, using the virus's genetic material when it is into the host cells to produce the antigen in each replication cycle. Viral vector vaccines can either be replicating, a kind of vaccine where the expression of antigen encoded is incorporated into the replication cycle or non-replicating, inducing the host immune response without replication inside the host cells. On the other hand, the DNA or RNA innovative technology platforms (nucleic acid vaccines) were applied. The DNA vaccine requires a successful transfer of the DNA followed by mRNA transcription to translate the antigen, while the RNA vaccine uses an mRNA molecule encoding the selected antigen. In both cases, an adjuvant is needed because of the instability of delivering naked RNA (Figure 2.11) (Pushparajah et al., 2021). Some of the technology platforms used by the pharmaceutical companies are described in Figure 2.12.
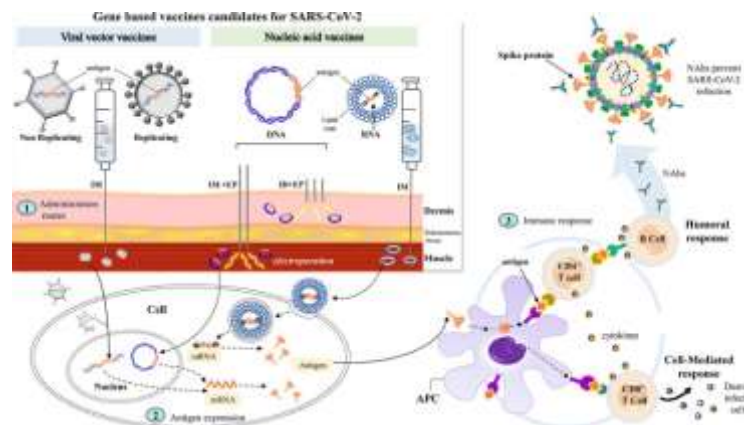
Figure 2. 11 COVID-19 vaccine platform (Pushparajah et al., 2021).

Pharmaceutical Company	Technology platforms used in the COVID-19 vaccine
Pfizer-BioNTech	mRNA
Moderna	mRNA
Oxford/AstraZeneca	Viral vector
J&J	Viral vector
Gamaleya (Sputnik V)	Viral vector
CanSinoBIO	Viral vector
Sinovac (CoronaVac)	Inactivated virus
Novavax	Protein subunit

Figure 2. 12 Technology platforms used in the COVID-19 vaccines (TrackVaccines, 2021).

Drug repositioning was one of the most valuable tools to fight the COVID-19 pandemic (Figure 2.13). In this case, many AI tools were applied to find a candidate to treat the SARS-CoV-2 using the Protein Data Bank (PDB), a worldwide database for macromolecular structures. In February 2020, the database opened a SARS-CoV-2 specific section, where almost 500 protein structures related to the virus has been elucidated and there are available for researchers. Availability of data to apply AI methods and time consumed in the evaluation before its publication is approved is a significant aspect to consider. (Dotolo et al., 2021).
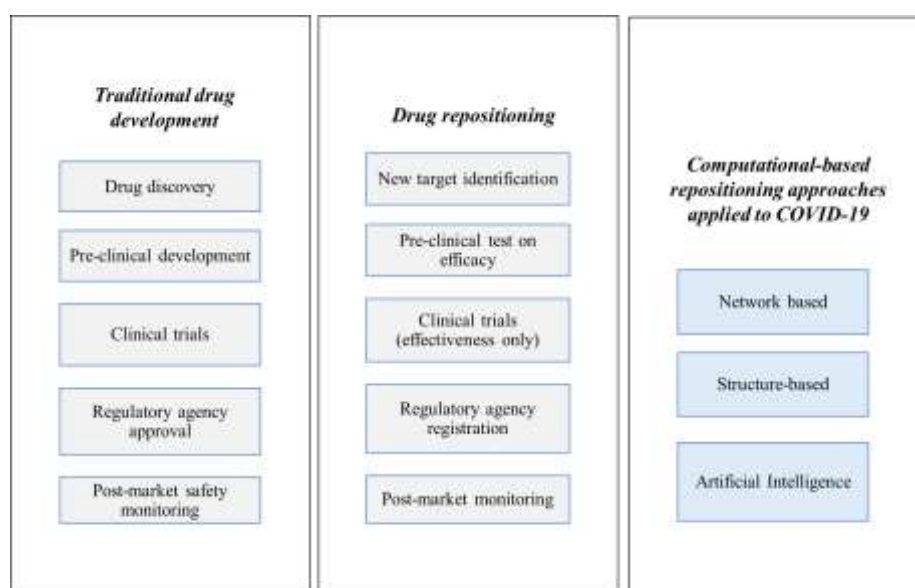
Figure 2. 13 Drug repositioning applied to COVID-19. Modified from (Dotolo et al., 2021).

2020 was a great year in the field of new drug approvals (NDA). Because of the virus, three new vaccines were emergency approved. In the Pfizer-Biotech COVID-19 vaccine, innovative technology was applied, which is based on mRNA technology. According to NDA, 51 new therapeutic drugs were approved in the EU, 71 in the US and 11 shared, concluding 133 new entities. Even though the approvals number in the EU increased, from 69 products classified as novel drugs, just 20 were developed in the EU. In this path, reaching for innovative technologies is essential to point out 63% of those therapeutic entities are from small and medium-size Pharma and 37% from Big Pharma (Figure 2.14) (NDA, 2021).

Figure 2. 14 Status of new Drug Product Approvals in 2020 (NDA, 2021).

Conceptual Framework

According to the finding from the literature review, the potential R&D innovative technologies and their possible challenges are summarized in the conceptual framework (Figure 2.15).
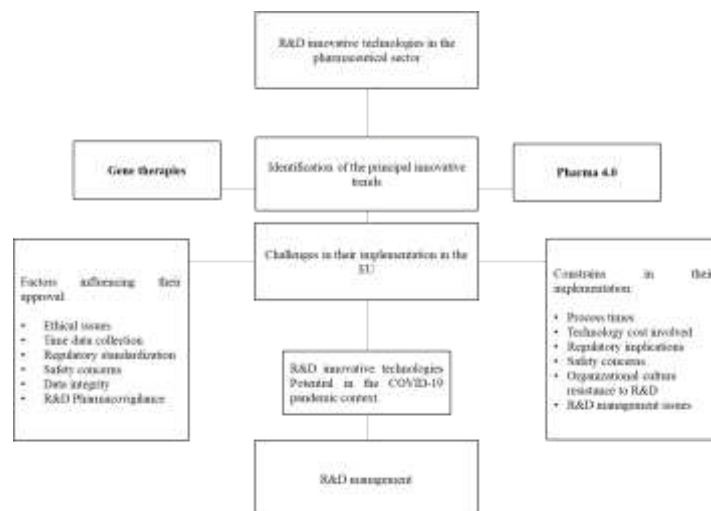
Figure 2. 15 Conceptual framework.

CHAPTER III

RESEARCH METHODOLOGY

2.1 Research Philosophy and Approach

The research philosophy is a practice of the theories unity in knowledge development. The philosophies could integrate three general assumptions. Firstly, the ontological assumption answers the nature of reality, while the epistemological assumption responds to the relationship between the researcher and the phenomenon to be studied. Finally, the axiological beliefs refer to the place of values in the research. Research paradigms follow assumptions and which they have two extremes; subjectivism and objectivist (Saunders et al., 2019).

The subjectivist extreme supports that social reality exists only as a product of personal understanding, creating concepts that help define reality. Individuals obtain knowledge from the subject under investigation (interpretative epistemology) and from individual experience. The most appropriate research methods will be those allowing the researcher to penetrate the internal worlds of individuals since the main interest of the research lies in knowing how the individual creates, modifies and interprets the world (qualitative methodology). As a result, ontological commitments come before epistemological and methodological (Al-Ababneh, 2020).

The objectivist extreme understands structures as concrete, empirical, independent, prior and extraneous to the individual knowledge (realist ontology). Therefore, individuals acquire knowledge through partial observation and fractional interpretation (positivist epistemology). Thus, methods of the natural sciences are applied to the location, explanation and prediction of social patterns and regularities (quantitative methodology) (Al-Ababneh, 2020).

Objectivism and subjectivist approaches support a philosophical stance, which precedes a research methodology determination. According to Saunders, there are five general research philosophies: positivism, critical realism, interpretivism, postmodernism and pragmatism (Figure 3.1):

Positivism: this current has the foundations of quantitative methodology. The answer to logical positivism is to test hypotheses probabilistically. Once they have been accepted and proven in different circumstances, the idea could develop general theories. Positivism views science as an attempt to codify and anticipate experience. It regards the scientific method as the only valid attempt at knowledge based on observational data and measurements of magnitudes and events. The base of logical positivism is the dogma of the universality of the scientific method. Theories and laws are developed to correlate observational data. Therefore, a valid theory is the best tested and fits all observational data, called the empirical theory. In the end, only those propositions whose truth can be established by observations are credible. In addition, positivism maintains a radical principle of distinction between science and non-science, which would be the application of a unique and universal scientific method. It consists of objective and universal rules for the design of experiments and the evaluation of theories that ensure success and progress (Alharahsheh et al., 2021; Saunders et al., 2019).

Critical realism: It claims that the world understanding is through events experienced and sensations, where reality is the most crucial consideration. It considers ontology assumptions and recognises epistemological relativism based on historical knowledge. Critical realism supports the subjectivist approach to knowledge, sustaining that notions of causality cannot be reduced to statistical correlations and quantitative methods, and some different techniques are acceptable (Saunders et al., 2019).

Interpretivism: It is a philosophy based on the naturalistic approach to data collection, such as interviews and observations. Interpretivism has two variants; hermeneutics and phenomenology. Hermeneutics regards the philosophy of interpretation and knowledge, and phenomenology is the philosophical idea that seeks to understand the world through the direct experience of phenomena. Relativist ontology, subjective epistemology and symbolic interactionism are the beliefs of the interpretivism approach. It would enable researchers to treat the context of the research, given circumstances associated and participants involved. This model would also support the investigation to be more focused on the specific topic and less generalisation as given in the positivist paradigm, where study sites, respondents or cases are selected based on theoretical considerations and fit the phenomenon under study (Alharahsheh et al., 2021; Saunders et al., 2019).

Postmodernism: It refers to the principles of modernity with a rational foundation based on communication, where postmodern thought is the set of philosophical approaches. Postmodernism investigates new interpretations of the social and the scientific environment and explains the relationship between what is produced and who produces it. It does not seek a complete explanation of reality. Postmodern research proposes qualitative research characterised by being inductive, naturalistic and interpretative. Inductive when they do not start from previous theories and hypotheses, they ask themselves some vague questions that guide them on the data to be collected. Naturalistic attempts to interact with the informants and the environment in a natural, non-intrusive way, without formalities that cause inhibiting effects on the people who provide the information. Interpretive, because it tries to understand the meaning of human actions from the frame of reference provided by the data (Saunders et al., 2019).

Pragmatism: It relates meaning to evidence, and this philosophy aims to contribute practical solutions. This current is interested in functional outcomes. The central part of the research strategy is the problem statement and the research question requiring adequate action to address the problem. It follows formal and informal rhetoric supporting that knowledge is always based on experience. In pragmatism, the acquired knowledge is a transition either objectivity and subjectivity (Kaushik and Walsh, 2019).
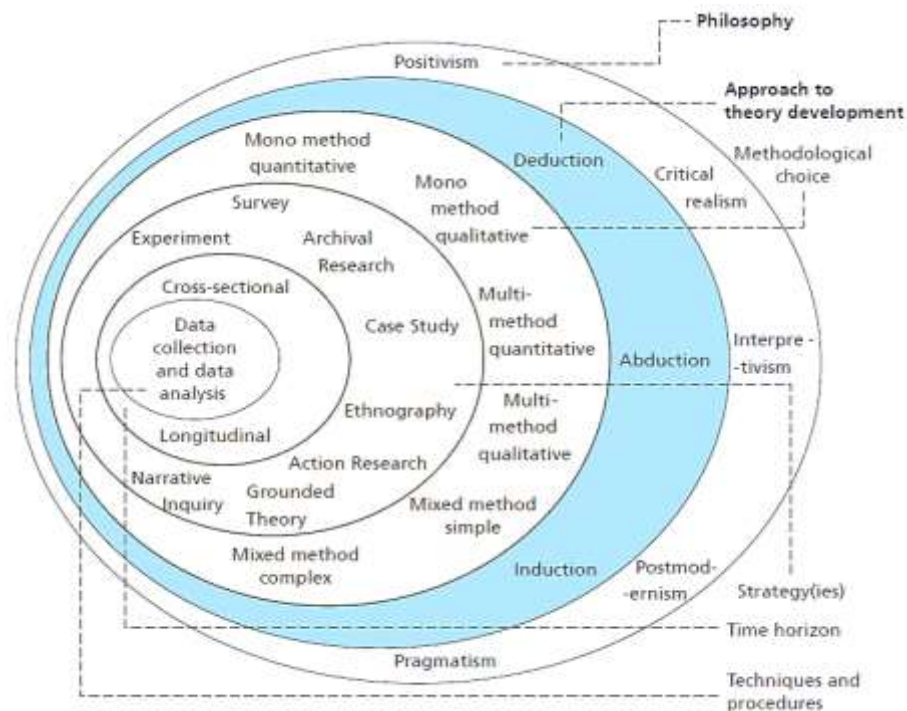
Figure 3. 1 The 'research onion' (Saunders et al., 2019).

In the research process, there are three fundamental approaches to generate theories (Figure 3.1):

Deduction: It is a conclusion derivation by reasoning when theories are generated through scientific research, and the data collection assesses the hypotheses.

Induction: It is an approach where information collection develops a theory and deducing a conclusion from particular instances.

Abduction: It involves creating a conclusion from the known information, where there is an inference of a case from a general rule and a result. It aims to generate an explanatory hypothesis for an empirical event (Saunders et al., 2019).

The present study follows positivism, critical realism and pragmatism research philosophies in evaluating the new trends challenges from different professionals perspectives in the pharmaceutical industry. Adopting positivism ensures unambiguity through the data assessment of R&D innovative technologies using a well-structured methodology, quantifiable comments and statistical analysis. The critical realism philosophy is helpful in the interpretation of professionals opinions working directly in areas implying in this research, supported by the fact that all those technologies are recently being used, the researcher could apply this philosophy. Pragmatism is followed in specific points because some of the regulatory, ethical and costly implications of those innovations could relate meaning to evidence and give practical solutions.

Induction and deduction approaches are being applied to evaluate the central hypothesis and assess the issues to uncover the challenges facing the new trends in R&D.

2.2 Methodology choice

The research method aims to gain knowledge through data collection, and the choice of the correct approach to gathering this information is crucial. Inductive and deductive methods have different objectives. These could be summarised as theory development and theory analysis, respectively. Inductive approaches are generally associated with qualitative research, while the deductive method is often associated with quantitative research (Strijker et al., 2020).

Quantitative research is an investigation in which quantitative data on variables are collected and analysed. Qualitative research avoids quantification. Researchers make narrative records of the phenomena in a study through techniques, such as participant

observation and unstructured interviews. The fundamental difference between the two methodologies is that quantitative research studies the association or relationship between quantified variables, and qualitative research does in structural and situational contexts. Qualitative research tries to identify the primary nature of realities, their system of relationships, their dynamic structure. Quantitative research attempts to determine the strength of association or correlation between variables, the generalisation and objectification of results through a sample to make inferences to a population from every sample is drawn. After the association or correlation study aims to make causal inferences that explain why things do or do not happen in a particular direction (Saunders et al., 2019; Strijker et al., 2020).

Regarding this information, this study has adopted a mixed methods research design following qualitative and quantitative approaches to investigated trends and challenges in pharmaceutical R&D.

2.3 Research Strategy

The search for bibliographic sources is based on the critical points of the study; R&D, Innovation and challenges in these fields in the European Union. As this research is based on current trends, it is always advisable to have up-to-date information. The main research engines are:

- Science Direct
- PubMed
- Google Scholar
- Griffith College Library
- Official pages of regulatory entities
- Official companies websites.

There are various possible strategies for conducting a research project, including a case study focused on deep investigation, experimental research through a methodological approach, quantitative survey a widely used method in business research accessing to significantly high numbers of participants, action-oriented research, in-depth interviews analysing exploratory participants ideas and documentary or archival research using available data information (Bazeley, 2017).

This research will follow survey research strategies and archival research. Many archival sources are currently available online, on official pharmaceutical company websites, regulatory body websites and high-quality academic web sides. The information will be obtained through archival research will be scientific articles related to new trends in research and development, those mentioning innovations in recent years and the challenges the pharmaceutical industry has faced in implementing these innovations. Keywords will include "innovation", "R&D", "challenges" and "Pharmaceutical industry".

The number of registered medicinal products approved by the European Medicines Agency will also be covered by this research strategy, using the EMA database. In the analysis, considering the R&D trends impact is in place, the cost, revenue, and losses will be obtained from the pharmaceutical companies official websites for the study. The most direct way to collect information, as primary research, will be through the networking tool LinkedIn, using contacts opinions by conducting a survey. A non-probability sample will be selected using volunteer sampling, and each participant can determine whether to participate in the research through surveys (Saunders et al., 2019). As the target population is unknown, this research expects to sample 30 surveys regarding the sample size.

The structure of the survey includes 22 questions (Appendix A). In the first section, the questionnaire is focused on the survey participant field to ensure the population has the knowledge and experience in the technologies being evaluated in this research. Secondly, the questions are oriented to the main challenges those trends could face and then evaluate geography implications in the investment of innovative technologies. Besides, some responses are being addressed explicitly to Pharma 4.0 and Gene therapies, while other participant responses attempt to uncover different implications and benefits. Finally, the questionnaire tries to estimate the future for those trends and their potential in the current COVID-19 pandemic.

The questionnaire is designed for professionals working or researching in the pharmaceutical sector across the European Union.

- Scientists; who work across of those innovative technologies helping them to develop new path in disease action mechanisms and its implication in the drug discovery stage.

- Regulatory Professionals; who can consider the key trends in R&D from a regulatory perspective, implications and ethical issues.
- Pharmaceutical professionals; who work day by day in the pharma industry, manage decisions, apply the technologies, and give an opinion from the research and development perspective.

Due to the covid-19 situation, interviews will be not conducted. Surveys will be online with professionals working in the research and development area, regulatory professionals related to the pharmaceutical industry, and professional scientists to support the initial objective of this study following an ethical research approach. This study will generate quantitative and qualitative data.

2.4 Time horizon

The time implied in a research project is classified into two general approaches. According to AI-Ababneh et al. (2020), they are:

Cross-sectional: it follows a positivistic methodology. The time for data collection is a short period, and it can be obtained from different contexts simultaneously, allowing the identification of correlations among variables.

Longitudinal: it is commonly used in a qualitative approach and allows the researcher to conduct research several times continuously (Al-Ababneh, 2020).

The cross-sectional approach is attended in this study because there is an established short time to conduct the research and determine correlations among responses.

The full research selection is in the Figure 3.2.

Research philosophy	Positivism	Critical realism	Pragmatism
Research approach	Inductive	Deductive	
Methodology	Mixed methods		
Research strategy	Archival research	Survey	
Time horizon	Cross-sectional		
	Data collection and data analysis		
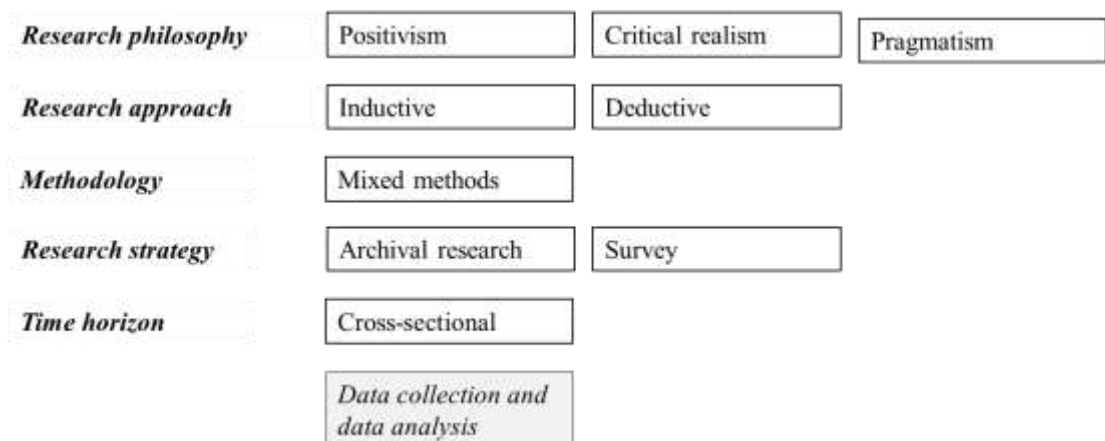
Figure 3. 2 Research methodology selection.

2. 5 Ethical Concern.

While doing research the ethical part cannot be overlooked and represents a vital role. It is essential to work with transparency and according to ethical principles.

Personal information is not required in this investigation, participation is voluntary, and the data collection is anonymous. This research avoids any cause of data inaccuracy, such as misrepresentation or fraud. Each survey has a respondent ID, an internet protocol address, date and time when they were filled. This study intends to be answered by real professionals, where their rights are considered. All participants are informed about the purpose of the study, and their consent to participation is required.

Under the understanding that the present research project has been conducted for academic purposes as part of the fulfilment for master program, the results of this research will be stored by the researcher and the university until the exam board confirms the results and retained for a maximum of seven years for publication purposes.

CHAPTER IV

DATA ANALYSIS

This chapter comprises the results obtained from the research conducted through a questionnaire and analysed accordingly to the research objectives. The data supports the investigation, and the insights are the basis to support or reject the research hypothesis.

4. Concise demographic data representation of the population

The research was conducted through a questionnaire distributed to people working in the R&D area, pharmaceutical professionals and regulatory experts. LinkedIn has been the tool used to contact 100 people working in those areas across the European Union. However, probably due to the time of the survey being during the holidays period, only 20 people answered the survey and a sample population of twenty participants has been achieved.

4. 1 Profession and highest level of education

The distribution of the participants accordingly to their profession, the highest level of education and work years of experience are shown in Table 4.1 and Figure 4.1.

Table 4. 1 Representation of the number of participants, the highest level of education and work experience.

Profession	Highest level of education			Years of experience					Total N° Rs	Frequency %
	B.A./ AdvDip	MS	PhD	NE	1-2 years	3-5 years	5-10 years	More than 10 years		
R&D	5%	15%	10%	10%	0%	10%	0%	10%	6	30%
Pharmaceutical professionals	5%	25%	20%	5%	10%	15%	0%	20%	10	50%
Regulatory professionals	5%	10%	5%	0%	0%	10%	5%	5%	4	20%

Among twenty professionals who responded to the questionnaire about R&D innovative technologies, 10 (50%) were working in the pharmaceutical industry, 6 (30%) were from

scientists working in R&D, and 4 (20%) were from the regulatory professionals field (Table 2.1). The highest number of responses was from pharmaceuticals professionals. The top level of education in that category was a Master Degree (25%), followed by professionals with a PhD (20%), and 5% hold a Bachelor Degree/Advanced Diploma. The general percentage according to the level of education of participants among the three categories have shown that most of them have the highest level of education, a PhD (50%), 35% have studied a Master Degree and 15% of respondents have B.A/AdvDip (Figure 4.1).
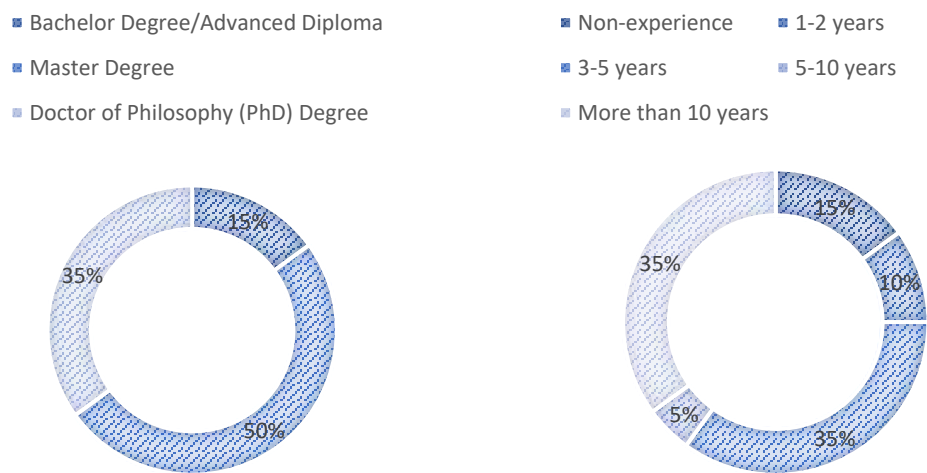
Figure 4. 1 Representation of the highest level of education and work experience percentage of participants.
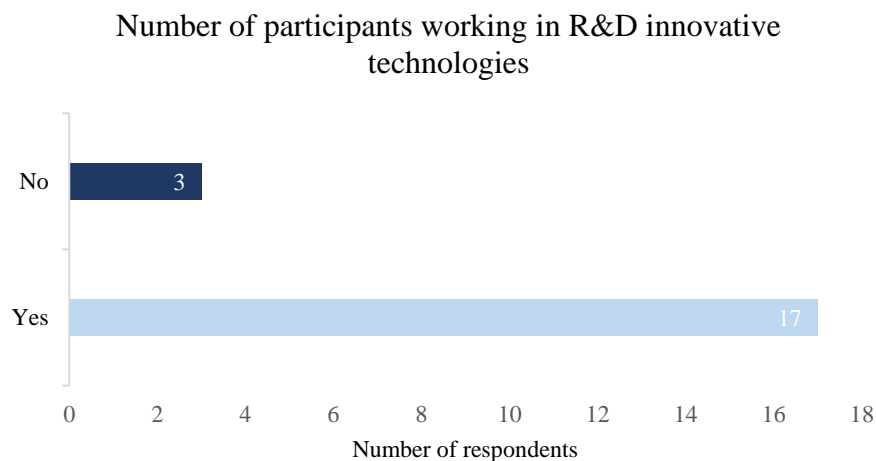
Figure 4. 2 Representation of participants working in R&D innovative technologies.

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Conforming to the data reported in Figure 4.2, most respondents have experience working with R&D innovative technologies due to seventeen people responded *"yes"*. The data has shown that people involved in new technologies have been working between 3 to 5 years and more than ten years (35% respectively), while 5% have non-experience (Figure 4.1). The general rate among the three working areas was 3-5 years and more than ten years, Scientists in R&D (10%/10%), pharmaceutical professionals (15%/20%) and regulatory professionals (10%/5%) (Table 2.1).

4.2 Evaluation of the objective 1. Identification of the principal trends in R&D, science and innovation in the EU pharmaceutical companies.

In order to assess the principal trends in the current context of the European Union, the questionnaire participants answered questions related to R&D innovative technologies which are having a period of prosperity, emerging, or are still being evaluated as an option of rapid economic growth to the future in the pharmaceutical sector. Those innovations include the fields of Gene therapies and Pharma 4.0.

Has your work place implemented any innovative technology in R&D, such as Gene therapies or Pharma 4.0, in the last five years?
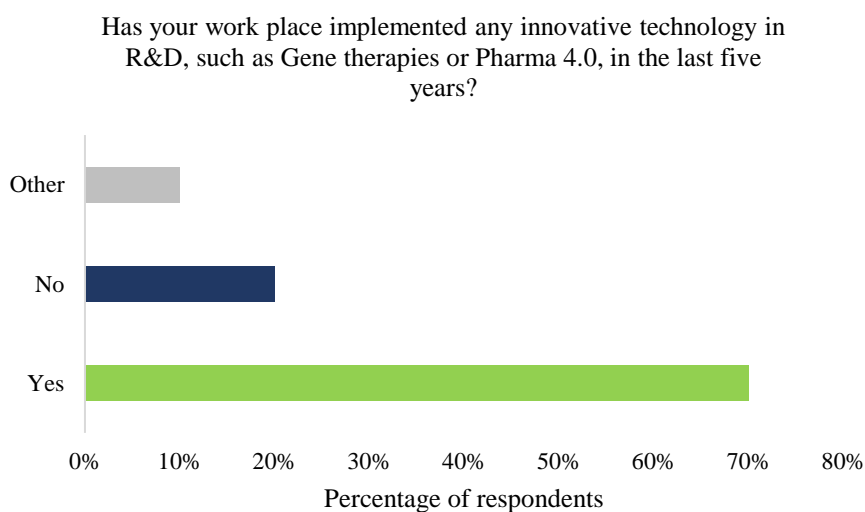
Figure 4. 3 Percentage of professionals who have implemented innovative technologies in R&D, such as Gene therapies or Pharma 4.0, in the last five years.

The professionals overall from three different areas were asked if they have implemented any innovative technology in R&D, such as Gene therapies or Pharma 4.0, in the last five years. 70% have implemented some of those technologies in their workplace, while 20% have not. 10 % of the respondents specify other, answering *"partially"* (Figure 4.3).

Data presented in Figure 4.4 shows that 45% of professionals agree that Gene therapies effectively treat autoimmune and cancer diseases, 25% support the statement strongly agreed, and 25% remain neutral. It corresponds to the greater percentage of viewpoints agreeing that the use of those therapies outweighs their risks (45%), while 5% strongly agrees, 10% disagrees, and the percentage of neutral increases to 40%.
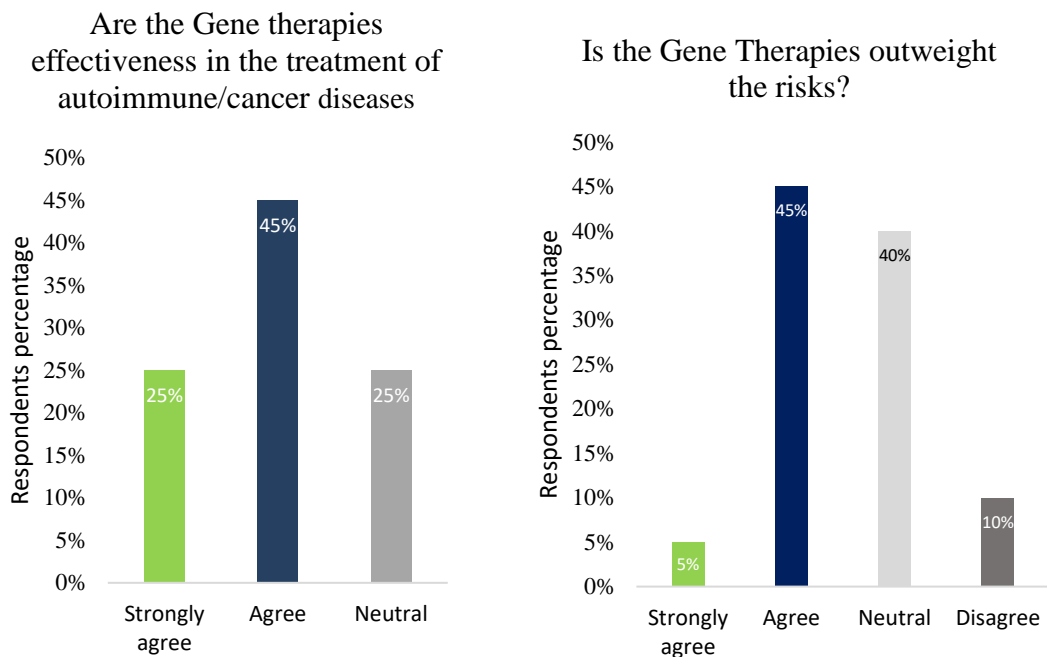
Figure 4. 4 Representation of respondents who agree or disagree about the Gene therapies effectiveness in treating autoimmune/cancer diseases, and comparison with people who agree or disagree with the statement that the Gene therapies outweigh the risks.

According to Table 4.2, the pharmaceutical sector has implemented different tools involved in "the fourth industrial revolution", Pharma 4.0. Following the digitalization era and the new trends, the Pharma 4.0 elements that have primarily been implemented across the regulatory area, the pharmaceutical industry and R&D have been Cloud-based data management (68.42%) and AI (57.89%), followed by Integration and traceability (47.37%), Lifecycle management and Advance analytics (42.11% respectively), Process Analytical Technology (PAT) (36.84%) and Quality-by-Design (AQdD) (15.79%). The 5% of the people from those fields have not implemented any Pharma 4.0 elements in recent years. In their responses, different elections of various elements were allowed. The participants made an overall of 60 multiple selections, and one responder skipped the question.

Table 4. 2 Pharma 4.0 elements implemented per working area.

Ps N°	Experience Sector	Lifecycle management	AI	AQbD	Integration and traceability	Advanced analytics	Cloud-based data management	PAT	None
1	*Regulatory area*				✓		✓		
2	*Regulatory area*	✓			✓		✓		
3	*Pharma industry*		✓	✓	✓	✓	✓	✓	
4	*Regulatory area*		✓						
5	*R&D*								✓
6	*Pharma industry*	✓		✓	✓	✓		✓	
7	*R&D*		✓		✓	✓			
8	*Pharma industry*								✓
9	*Pharma industry*	✓		✓	✓	✓	✓	✓	
10	*Regulatory area*	✓	✓		✓		✓		
11	*Pharma industry*	✓						✓	
12	*R&D*	✓	✓		✓		✓		
13	*Pharma industry*	✓	✓			✓	✓	✓	
14	*Pharma industry*		✓				✓		
15	*R&D*		✓			✓	✓		
16	*Pharma industry*						✓		
17	*R&D*		✓						
18	*Pharma industry*	✓	✓				✓		
19	*Pharma industry*		✓		✓	✓	✓	✓	
20	*R&D*				✓		✓	✓	
	Total	42.11%	57.89%	15.79%	47.37%	42.11%	68.42%	36.84%	5.26%

Considering the independent answer from 60 answers, the Pharma 4.0 elements of response frequency was calculated based on the 19 responders. Figure 4.5 represents the same progression, Cloud-based data management (22%), AI (18%), Integration and traceability (15%), Advanced Analytics and Lifecycle management (13% respectively), PAT (12%), AQbD (5%) and 2% none.

Pharma 4.0 elements implemented
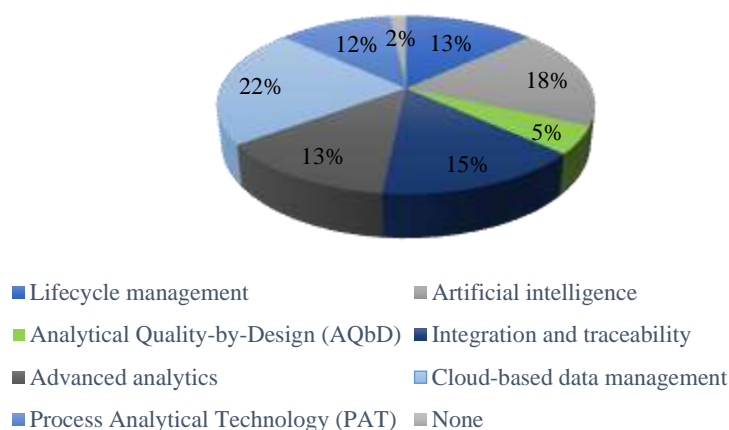
Figure 4. 5 Representation of the Pharma 4.0 elements implemented per working area.
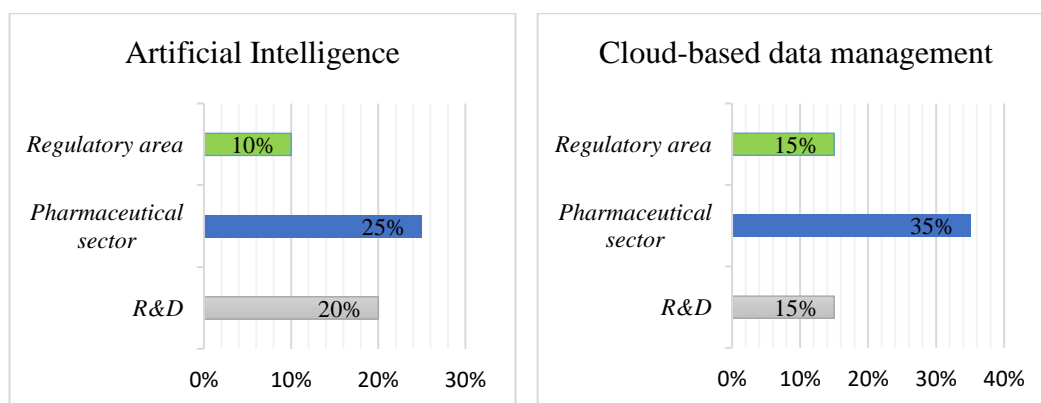
Figure 4. 6 Distribution of the two Pharma 4.0 tools more frequent applied in the last five years per working area.

Furthermore, to continue evaluating the pharma 4.0 elements implementation in the R&D, an statistical analysis was conducted comparing responses from scientists working in R&D, regulatory professionals and pharmaceutical professionals to assess the area where those elements are more often implemented (Figure 4.6). The AI implementation comparison with the Anderson-Darling Normality Test to compare the data distribution (Minitab) among the three categories was not significantly different, p-value > 0.5 (0.487) (Figure 4.7).
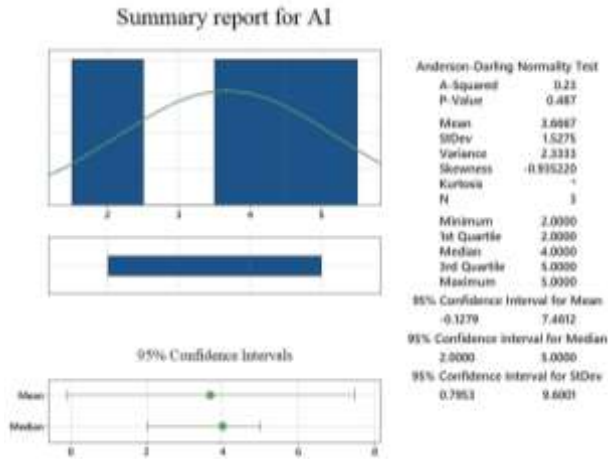
Figure 4. 7 Statistical AI applied comparison among R&D, Pharmaceutical industry and regulation area.

Consequently, there is no area where AI is more often implemented. In the following comparison, the Cloud-based data management was not significantly different, p-value > 0.5 (0.057), similar to the AI element comparison. It states 95% confidence the data does fit the normal distribution, showing that the Cloud-based data management element is not more often implemented more in the pharmaceutical industry (35%) than the others, Regulatory area (15%) and R&D (15%) (Figure 4.8).
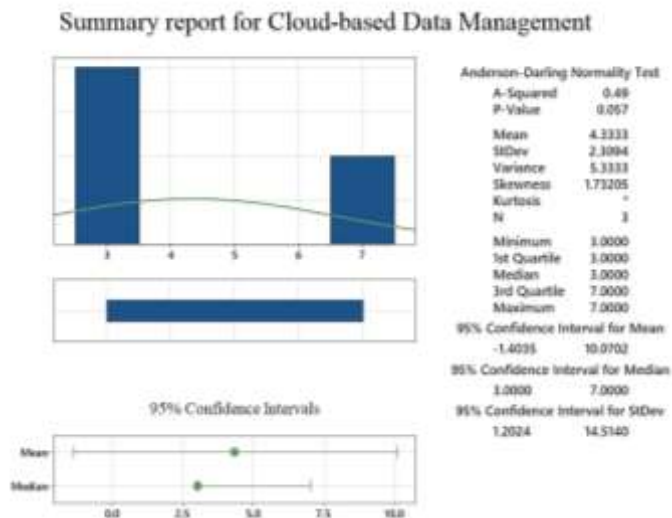
Figure 4. 8 Statistical Cloud-based data applied comparison among R&D, Pharmaceutical industry and regulation area.

Different opinions were obtained from the questionnaire. Three people (15%) from the twenty respondents provided additional information, sharing their general perceptions about the relevance of embracing innovation on pharmaceutical R&D (Table 4.3).

Table 4. 3 General perceptions about the relevance of embrace innovation on the pharmaceutical R&D.

Professionals comments about the relevance of embrace innovation in the pharmaceutical R&D.
General perceptions
"The digital transformation of the life science sector is critical to maintaining these sectors in Ireland through enhanced competitiveness and the realisation of sustainability targets. The digital transformation of the island of Ireland will be the re-definition of our island for the next 50 years. The pace of adoption needs to accelerate significantly if we are to compete with economies like China, India, Singapore."
"Embrace innovation is the smartest decision for the pharmaceutical industry in the current Covid-19 pandemic and future prevention."
"Organization will need to be flexible enough to integrate new technologies in their pipelines. Understanding the limits of new tech and that they might fail in the first attempts."

4.3 Evaluation of the objective II. Analysis of the R&D innovative practices and their main challenges in the current landscape.

According to what was previously mentioned in the Literature Review chapter, most innovative technologies have been facing some difficulties or challenges in their implementation. To evaluate objective II in this research, the scientists working in R&D, regulatory professionals and pharmaceutical professionals respond to questions associated with the factors influencing the R&D innovative technologies approval. Responders considered the Regulatory standardization (75%) the primary factor affecting the process, while Time data collection is the factor with less influence (20%). The 50% of professionals agree that safety concerns and ethical issues affect the new technologies approval (55% and 50% respectively), Data integrity (60%), and R&D

pharmacovigilance issues (8%) stay at the bottom. Some participants stand neutral; ethical issues 3(15%), Time data collection 4(20%), Regulatory standardization 4(20%) and R&D Pharmacovigilance issues 1(5%) (Table 4.4). Three people disagreed that ethical issues (5%), Time data collection factors (2%) and R&D Pharmacovigilance (5%) are impacting the new technologies approval (Figure 4.9).

Table 4. 4 Factors influencing the R&D innovative technologies approval.

Factors	Strongly agree	Agree	Neutral	Disagree	Strongly disagree	N/A
Ethical issues	10	6	3	1	0	0
	(50%)	(30%)	(15%)	(5%)	(0%)	(0%)
Time data collection	4	8	6	2	0	0
	(20%)	(40%)	(30%)	(10%)	(0%)	(0%)
Regulatory standardization	15	1	4	0	0	0
	(75%)	(5%)	(20%)	(0%)	(0%)	(0%)
Safety concerns	11	9	0	0	0	0
	(55%)	(45%)	(0%)	(0%)	(0%)	(0%)
Data integrity	12	4	4	0	0	0
	(60%)	(20%)	(20%)	(0%)	(0%)	(0%)
R&D Pharmacovigilance issues	8	6	5	1	0	0
	(40%)	(30%)	(25%)	(5%)	(0%)	(0%)
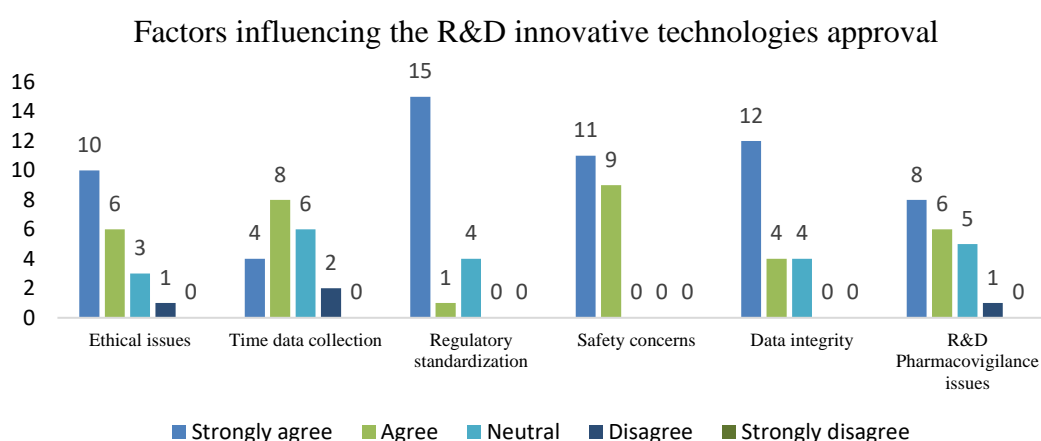
Figure 4. 9 Representation of the factors influencing the R&D innovative technologies approval.

Following the factors associated with the approval, there are constraints in the implementation of innovative technologies (Table 4.5). The regulatory implications (63.16%) and safety concerns (50%) were the highest strongly agree percentage of respondents opinions. The 40% of professionals consider the Technology cost a limitation, 45% agreed, 5% remain neutral, and the 10% do not evaluate it as a constrain. Responders had been strongly agreed that Process times (35%) affects the implementation of new technologies, while the 15% had disagreed. Professionals agreed that the Organizational culture resistance to R&D change (35%) and the R&D management (20%) has less influence in implementing innovative technologies. Two people (10%) disagree about this statement (Figure 4.10).

Table 4. 5 Constrains in the implementation of innovative technologies.

Constrains	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Process times	(35.00%)	(30.00%)	(20.00%)	(15.00%)	(0.00%)
	7	6	4	3	0
Technology cost involved	(40.00%)	(45.00%)	(5.00%)	(10.00%)	(0.00%)
	8	9	1	2	0
Regulatory implications	(63.16%)	(26.32%)	(10.53%)	(0.00%)	(0.00%)
	12	5	2	0	0
Safety concerns	(50.00%)	(40.00%)	(10.00%)	(0.00%)	(0.00%)
	10	8	2	0	0
Organizational culture resistance to R&D change	(35.00%)	(15.00%)	(40.00%)	(10.00%)	(0.00%)
	7	3	8	2	0
R&D management issues	(20.00%)	(40.00%)	(30.00%)	(10.00%)	(0.00%)
	4	8	6	2	0
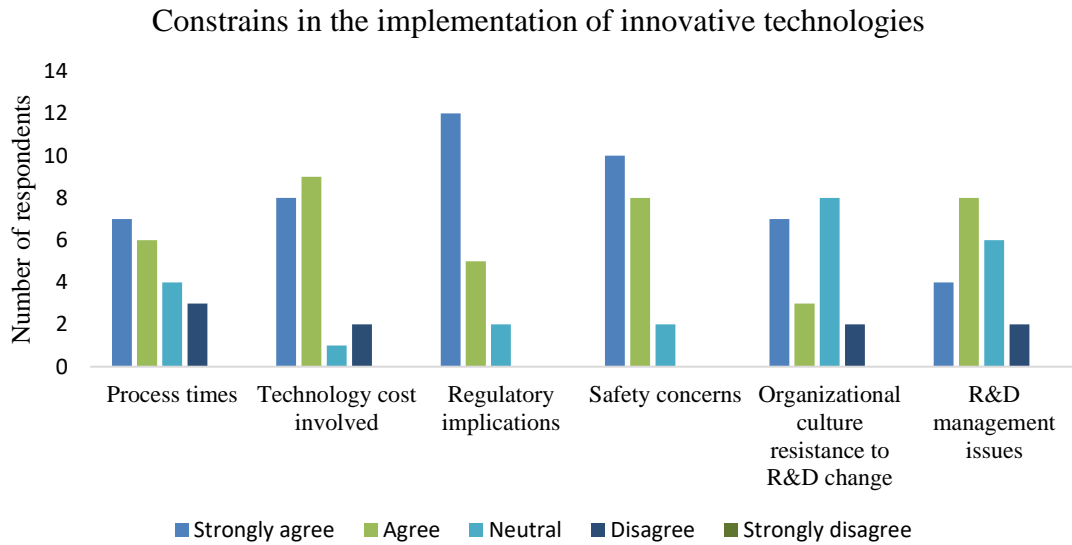
Figure 4. 10 Representation of the constrains in the implementation of innovative technology.

The responders elaborated answers about how regulatory differences between countries significantly impact the implementation of R&D innovative technologies. Four of them stated, *"The approval of new therapies is subject to their respective regulatory entity. The speed in the approval time will depend on the individual regulatory entity such as FDA, EMA."* Another opinion claims, *"Regulatory rules driven by countries can play a vital role in the time of innovative technologies approval."* A regulatory professional responded, *"If the industry knows that a potential product - however innovative or life-changing it can be- has high chances of not getting regulatory approval (for various reasons) in the major markets, the industry will not progress with it. It has to be taken into consideration that other (less major) markets tend to 'follow' the approvals from approvals gained from the major markets (US, EU, Japan, China)."*

Finally, a responder stated, *"Differences in regulatory requirements and regulatory agencies cause small R&D innovations to be located in countries with clear, concise and timely approval procedures".*

As a consequence of the various challenging factors in the R&D innovative technologies, a high cost is implied in their implementation because it consists of many actions to achieve high quality and safety across the process to reach effective therapy. To the degree that additional support can perform an essential role for innovative technologies, professionals were asked about the governmental funding from their countries over the

European Union. This question aimed to obtain knowledge about the EU support for the R&D innovative technologies. The results obtained from six responders are shown in Table 4.6.

Table 4. 6 Countries member of the EU and the governmental funding/support for innovative technologies.

Country	Governmental founding
Ireland	- Disruptive Technology and Innovation Fund (DTIF)
Sweden	- Vinnova Fund - Advanced Therapy Medicinal Products (ATMPs) support
France	- Bourse French Tech
Denmark	- Innovation Fund Denmark
Germany	- State and Country funding
Belgium	- Agency for Innovation and Entrepreneurship (VLAIO) funding

4.4 Evaluation of the objective III. Evaluation of the potential of innovative R&D technologies in the COVID-19 pandemic context.

According to the Literature Review chapter, the R&D innovative technologies extends the opportunities in the pharmaceutical sector. Further analysis was conducted to evaluate the potential of those technologies in the current COVID-19 context. As a challenging time, the COVID-19 pandemic demanded innovation embracing new trends and bringing the R&D to the digitalization era. Faster solutions are required for unpredictable events to the benefit of people health. In agreement with this point, professionals were asked if implementing R&D innovative technologies in the pharmaceutical sector confers an advantage in a COVID-19 pandemic. People who agree with the question were 55%, 40% strongly agree, and 5% remain neutral. None of the respondents in the three areas: R&D, pharmaceutical industry and regulatory professional disagreed with the statement (Figure 4.11).

Does the implementation of R&D innovative
technologies in the pharmaceutical sector confers an
advantage in a COVID-19 pandemic context?
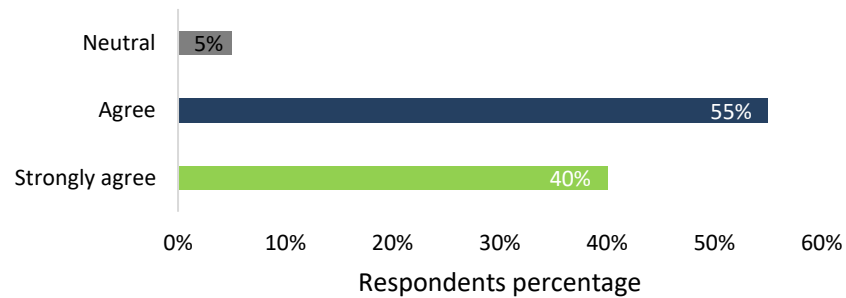
Figure 4. 11 Representation of people who agree or disagree about R&D innovative technologies implementation in the pharmaceutical sector confers an advantage in a COVID-19 pandemic context.

A significant percentage of professionals (55%) believe that elements such as AI in R&D improve the entire product development lifecycle with access to big data in real-time, the 35% is agreed with that statement, while 10% remain neutral (Figure 4.12).

AI in R&D improves the entire
product development lifecycle with
access to big data in real-time

Figure 4. 12 Distribution of professionals viewpoints about the product development lifecycle improvement using AI.

Different opinions were aimed from pharmaceutical professionals, regulatory professionals and scientists working on R&D, about the potential of those new technologies in the COVID-19 pandemic context in the EU shown in Table 4.7. In general, the nine responses were positive perceptions.

Table 4. 7 General perceptions from pharmaceutical professionals, regulatory professionals and scientists working on R&D, about the potential of R&D innovative technologies in the COVID-19 pandemic context.

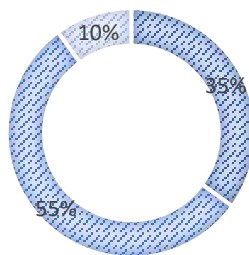| R&D innovative technologies in the COVID-19 pandemic |
|---|
| General perceptions |
| **Pharmaceutical Professionals** |
| *"R&D Innovative Technologies that enable Digital Transformation of a development/manufacturing site can absolutely bring products to the market quicker, through real-time sharing of data, self-guided or remote-managed manufacturing processes and information sharing."* |
| *"Covid-19 has almost opened the door on more technologies being considered, as industry has seen approvals based on the need of the public."* |
| *" The pharmaceutical innovation or the upgrading compared to other market sectors is not as quick as it should be, this might be due to the regulation factor involved in implementing a change. But clearly implementing innovative technology is the solution for most of the problems the industry is facing today."* |
| **Regulatory Professionals** |
| *"Innovation increase the patients opportunity to have access to high-quality and effective medicines."* |
| *"Faster responses in the Covid-19 pandemic is the result of innovations."* |
| **Scientists in R&D** |
| *"Implementing the R&D innovative technologies to assist in eradicating the current pandemic (i.e. faster vaccine production and rollout) is definitely advantageous."* |
| *"R&D tech is essential for good long term pandemic responsiveness. However, unless matched with regulatory flexibility and financial incentives toward preparedness for the next pandemic, such technology will have limited real world benefit."* |
| *"mRNA vaccines can be considered an innovative technology. Plus AI/ML helped the development of vaccines and are used to search new drugs against covid."* |
| *"New technology increases the possibilities to find a new drug entity to treat a disease. In this context where the world was waiting for a quicker response having tools such as AI or real-time data access allow better research communication and cooperation."* |

R&D constantly has been a word related to innovation, and innovation creates a picture forward. In this research, looking for the future of the R&D innovative trends in the following years, professionals have responded about what they consider will be the major challenge in the Pharma R&D in the next ten years. The most serious concern was Data integrity and cybersecurity (25%) as well as Policy and regulatory activity (25%), followed by Digital therapeutics and personalized medicine (20%), Advances in technology (10%), Adequate return on innovation (10%) and Ethical issues and safety concerns (5%) (Figure 4.13).

Major challenges in the Pharma R&D in the next 10 years
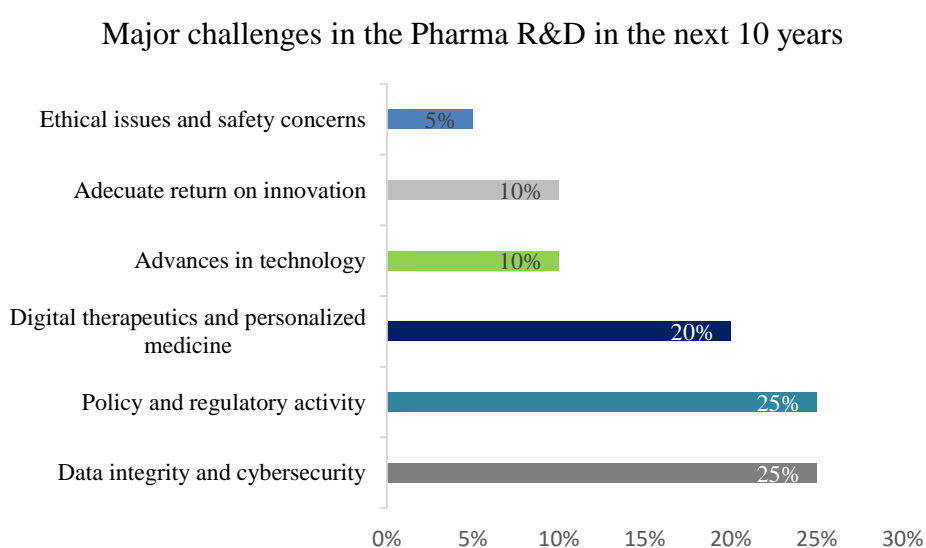
Figure 4. 13 Graphical description of the major challenges in the Pharma R&D in the next 10 years.

In this landscape where the R&D is driving innovation, leadership through executive direction and management presents an essential role in adopting new technologies. Pharmaceutical professionals, regulatory professionals and scientists working on R&D were asked about the importance of R&D management in implementing new technology. Nine responses through the three categories of professionals gave positive general perceptions, and one of the responders claims the priority of management in two words, it is "very crucial" (Table 4.8).

Table 4. 8 R&D management in the implementation of new technology.

R&D Management in the implementation of new technology
General perceptions
Pharmaceutical Professionals
"R&D management i.e. the development of these technologies is key to getting these technologies to the market as soon as possible."
"R&D management can help support the implementation by doing and in-depth analysis on how new technologies can affect any/every research overall, and hence can encourage other researchers to try out the new technologies."
"R&D management monitors trends, establishes partnerships and collaborations (and therefore must see the initial promise of such relationships), navigates relationships with regulatory affairs, and crafts messages to healthcare providers to translate the innovation into practice."
"While the R&D department may see the value of a new technology, it requires buy-in from the rest of the business from funding and there is often hesitation."
"All the development factor depends on effective R&D as this is the factor that drives the Pharmaceutical towards a possible solution for most of the diseases etc."
"Very crucial."
Regulatory Professionals
"Good leadership supports innovation and encourage scientists to move to new technologies."
Scientists in R&D
"Management needs to embrace new technologies but also understand their limitations. They have to encourage people to use new technologies whenever is possible."
"Absolutely, leadership and well management in R&D allow access to more research sources and implementation."

CHAPTER V

DISCUSSION AND DATA ANALYSIS

This research has been conducted to assess R&D innovative technologies in the pharmaceutical sector and subsequently have evaluated the implementation challenges across the European Union. The study has covered an examination of new technologies, such as Gene therapies and Pharma 4.0

Several studies have shown that the general working areas related to R&D innovation are researchers (scientists working in R&D) and people involved in daily activities of R&D in the pharmaceutical environment (pharmaceutical professionals). Besides, specialists working in the approval and well regulation guarantee high-quality and safety of innovative trends concerned in the drug discovery and development (regulatory professionals) (Cassanelli et al., 2017; Drago et al., 2021; Reinhardt et al., 2020). This study has considered their professional knowledge and experience to support this research.

The first objective has attempted to identify the principal trends in R&D, science and innovation in the EU pharmaceutical sector. In line with the results, the most significant participation from professionals involved in R&D innovative technologies was from pharmaceutical professionals (50%) being master degree holders (25%) with a high level of experience in the field, working for more than ten years (20%). The professionals recognise Gene therapies and Pharma 4.0 elements as R&D innovative technologies implemented in the current landscape, based on the data analysis section 4.2. Moreover, people involved in the research identify Lifecycle management, AI, AQbD, Integration and traceability, Advanced analytics, Cloud-based data management and PAT as Pharma 4.0 elements implemented in recent years in the European Union being agreed with some studies that mentioned the implementation of those technologies worldwide (Aceto et al., 2020; Barenji et al., 2019; Gupta et al., 2021).

Interesting findings were discovered in the evaluation of the more prevalent element implemented. According to the data, the European R&D new technologies in the Pharma sector is driving innovation. 70% of professionals, who participated in the study, have been implemented innovative technology in the last five years (Figure 4.3). The popularity of Artificial Intelligence and Cloud-based data management among the R&D

area, pharmaceutical sector, and Regulatory area lead the list of the Pharma 4.0 elements implemented in the EU latterly (Figure 4.6). Even though several studies have reported the widespread use of AI in the early stages of drug development in the research of lead compounds in the drug discovery stage (Gupta et al., 2021), the results from the Anderson-Darling Normality Test have not shown that the use of AI and Cloud-based data management have significant difference among areas. However, as the sample was small, there might be differences with a bigger sample.

General thoughts from professionals' perceptions invite to embrace innovation. Respondents mention that in some countries of the EU, such as Ireland, the digital transformation of the life science sector is critical to enhancing competitiveness and sustainability targets to stand to the world powers in line with studies that have shown that digitalization is transforming the economy (Romanova and Kuzmin, 2021). However, it is essential to understand the limits, scopes and difficulties of those technologies. This statement leads to the second objective of the research.

The purpose of the second objective has been to evaluate the main challenges of the R&D innovative technologies. From the short review about approvals and implementation of technologies concerning the Gene therapy field or Pharma 4.0, various investigations suggest factors and constraints in their license and implementation.

Firstly, as reported by Safarzadeh Kozani et al. (2021) and Zaami et al. (2021), there are several side effects in the applicability of Gene therapies, such as cytokine release syndrome, efficacy shortcomings and neurotoxicity in CAR-T cells explained in the Literature Review chapter. Besides, the critical ethical implications in the use of CRISPR (Safarzadeh Kozani et al., 2021; Zaami et al., 2021). According to Figure 4.4 data in the previous chapter, responders claim in favour of those innovative technologies in the EU, supporting that the effectiveness of Gene therapies in the treatment of autoimmune and cancer diseases and the statement that their benefit outweigh the risks in conformity to other studies such as Li et al. (2021) and Hosseini et al. (2021). It is important to point out that some people remain neutral about this topic (Hosseini et al., 2021; LI et al., 2021). Ethical implications such as making public the technology implications, safety, reliability assessment of the therapy and responsibility have to be considered. However, it was not within the scope of this dissertation.

Secondly, in Pharma 4.0, recent reports have shown that digitalization is a reality, and factors such as high cost in some technologies such as AI could be a limitation in their implementation. However, the great concern for more areas involved in the regulation side to prevent harm and guarantee data integrity and safety across all processes (Aceto et al., 2020; Gupta et al., 2021; Kumar et al., 2020)

In this research, considering the mentioned implications, the professionals responses about the factors involved in the approval and the constraints in implementing those R&D innovative technologies in the EU environment have led to similar results. The Regulation standardization represents the more significant factor influencing the R&D innovative technologies approval such as Gene therapies and Pharma 4.0 in the EU. The biggest constrain following the Regulatory standardization in implementing those technologies is Data Integrity and Ethical implications, according to the results in Table 4.4/4.5. Participants opinions share the thought that even though an innovative therapy has potential, it has high chances of not getting regulatory approval if it compromise patient safety.

Respondents strongly agreed that one more constraint to consider is the Technology cost. A report published by Cambridge university mentioned that the affordability of technologies in drug development represents a public health problem because some technologies such as CAR-T are highly costly, and public and non-profit contributions to drug development are needed (Sarpatwari and Kesselheim, 2021). In this context, six respondents identified a governmental funding to support R&D innovative technologies from different countries over the EU, implying that technologies such as Gene therapies and Pharma 4.0 can find funding in their implementation thanks to these programs.

Research and development drive innovation to improve therapies or develop new pipelines to bring a new product to the market. However, facing a crisis, innovation performs a principal role. In the current circumstances of the COVID-19 pandemic, the government have prioritized public health, increasing collaborations to develop the quickest treatment to fight SARS-CoV-2 (Agarwal and Gaulé, 2021b; Azoulay and Jones, 2020; Dotolo et al., 2021).

The final objective has been to evaluate the potential of innovative R&D technologies in the COVID-19 pandemic context. Professionals strongly agreed that implementing R&D innovative technologies in the pharmaceutical sector confers an advantage in the COVID-

19 pandemic. The highest rate of responders thinks the AI in R&D improves the entire product development lifecycle with access to big data in real-time. It supports the idea that in a disease outbreak, such as COVID-19, access to big data can enable monitoring it in real-time. Besides, open-access datasets and hundreds of structures allows for repositioning in the current pandemic (Bragazzi et al., 2020; Dotolo et al., 2021).

Pharmaceutical professionals consider the COVID-19 pandemic has opened the door on more technologies being considered and implementing innovative technology is the solution for problems the industry is standing today. Regulatory professionals stand that innovation allows the achievement of high-quality medicines, and scientists working in R&D support that the mRNA vaccines have been such an example of innovative technology. Based on the perceptions description in Table 4.7

In this disruptive time, the world is looking forward to the future of the R&D innovative technologies and their significant challenges in the next ten years in the EU. In agreement with what the responders consider, the major challenge in the following years will be Policy and regulatory activity and Data integrity and cybersecurity. According to the pharmaceutical strategy for the EU, the collaboration will increase in the European Union, working in the development, approval and access to the product lifecycle and improved availability and affordability. It will include the adoption of health technology assessment regulation based on innovation (Draguet, 2020).

The response to the COVID-19 crisis has provided hope for the innovation future through management processes and R&D management activities embracing technological development. Several R&D laboratories worldwide drove innovation to develop treatments and vaccines. According to Di Minin et al. (2021), 133 papers about the R&D management contributions to fight COVID-19 were submitted (Di Minin et al., 2021). Responders support the statement that the leadership represents an essential role in adopting new technologies, monitoring trends, encouraging collaborations and bringing the innovative technologies to practice. In the recent COVID-19 pandemic future, the organizations will require more strategic planning where greater talent about new technology and lead is vital (Kelleher et at., 2020).

CHAPTER VI

CONCLUSION AND RECOMMENDATIONS

6.1 Research conclusions

- Innovative technologies are disrupted the status quo of classical the research and development focus in the pharmaceutical sector within Gene therapies and Pharma 4.0.

- Gene therapies might be effective in autoimmune/cancer diseases, outweighing the risks implied. However, further research is needed.

- The principal Pharma 4.0 elements implemented in the EU in the last five years are Lifecycle management, AI, AQbD, Integration and traceability, Advanced analytics, Cloud-based management and PAT.

- Cloud-based data management and Artificial intelligence are the most used Pharma 4.0 elements in the R&D, Pharma industry, and regulatory areas in recent years.

- Regulation standardization is the most challenging factor influencing the R&D innovative technologies approval such as Gene therapies and Pharma 4.0 in the EU. Regulatory differences between countries have an impact their approval.

- Regulation standardization represents the major constraint in implementing new technologies, while Technology cost is the second most significant constraint.

- The current application of Artificial Intelligence in R&D improves the entire product development lifecycle with access to big data in real-time.

- R&D innovative technologies have potential in the COVID-19 pandemic. It represents an opportunity to have access to high-quality and effective medicine.

- Policy and regulatory activity, data integrity, and cybersecurity will represent the significant challenges in Pharma R&D in the next ten years.

- R&D management encourage researchers to try out the new technologies and support their implementation in the organization, performing a principal role in innovation.

6.2 Recommendations

- The population sample is not necessarily representative of the whole EU pharmaceutical sector. This research has been limited activity due to the short time of questionnaire disclosure. For the research, one hundred professionals working in R&D, Pharma industry and the regulatory area across the European Union were contacted. However, probably due to the time of the survey being during the holidays period, only a small sample population answered the questionnaire.

- The scope of this research was expected to analyse the current therapies approved related to R&D innovative technologies and their relation with the research and development investment of the top innovative companies by archival research. Due to time constrains, it was limited.

- Further research exploring ethical implications of Gene therapies and specific R&D management indicators in innovation might add additional value to this exciting topic.

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APPENDICES

Appendix A. The questionnaire structure that was carried out with scientist working on

R&D, regulatory professionals, pharmaceutical professionals.

QUESTIONNAIRE

R&D innovative technologies in the pharmaceutical sector and the challenges in their implementation in the EU

This questionnaire is carried out by Berenice Erreguin Luna, a MSc student at Griffith College Dublin and will take approximately 7-10 minutes.

The purpose of this survey is to evaluate the principal trends in R&D, science and innovation in the pharmaceutical sector and their current challenges in the EU, considering the recent landscape and the perspectives of pharmaceutical and biopharmaceutical professionals. The analysis aims to lay out the challenges for new technologies such as Gene therapy and Pharma 4.0 in the R&D area.

Your participation in this research study is voluntary, and the collected data will be kept anonymous.

Thank you very much for your time and participation.

*Required

Please, select the appropriate answer for each question below.

1. Do you understand the reason for the research? *
   a) Yes
   b) No

2. Do you consent to participate? *
   a) Yes
   b) No

3. Level of education:
   a) Bachelor Degree/Advanced Diploma
   b) Master Degree
   c) Doctor of Philosophy (PhD) Degree
   d) Other (please specify)

4. Does your experience involve working with Research and Development of innovative technologies?
   a) Yes
   b) No
   c) Other (please specify)

5. In which sector do you currently work?
   a) R&D
   b) Pharmaceutical sector
   c) Regulatory area

6. How many years of experience in the pharmaceutical sector do you have?
   a) Non-experience
   b) 1-2 years
   c) 3-5 years
   d) 5-10 years
   e) More than 10 years

7. Do you agree that the following factors can influence the approval of innovative technologies in the EU?

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
Ethical Issues						
Time Data Collection						
Regulatory Standardization						
Safety Concerns						
Data Integrity						
R&D Pharmacovigilance Issues						

8. Do you agree that the following constraints can influence the implementation of innovative technologies in the EU?

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree	N/A
Process times						
Technology cost involved						
Regulatory implications						
Safety concerns						
Organizational culture resistance to R&D change						
R&D management issues						

9. Is there any governmental research funding in your country for the development of new technologies such as Gene therapies or Pharma 4.0?
   a) Yes
   b) No
   c) Other (please specify)
   9.b If yes, please specify your country and the type of governmental funding.

   _____

10. Do you agree or disagree with the statement that regulatory differences between countries have a significant impact on the implementation of R&D innovative technologies?
    a) Strongly agree
    b) Agree
    c) Neutral
    d) Disagree
    e) Strongly disagree
    f) Other (please specify)
    10.b Please elaborate, giving reasons for your answer where possible.

    _____

11. Has your workplace implemented any innovative technology in the R&D process, such as Gene therapies or Pharma 4.0, in the last five years?
    a) Yes
    b) No
    c) Other (please specify)

12. Do you agree or disagree with the statement that Gene therapies are effective for the treatment of autoimmune/cancer diseases?
    a) Strongly agree
    b) Agree
    c) Neutral
    d) Disagree
    e) Strongly disagree
    f) Other (please specify)

13. Do you agree or disagree with the statement that the benefits of Gene therapies outweigh the risks?
    a) Strongly agree
    b) Agree
    c) Neutral
    d) Disagree
    e) Strongly disagree
    f) Other (please specify)

14. Will Artificial Intelligence in R&D improves the entire process of product development lifecycle with access to big data in real-time?
    a) Strongly agree
    b) Agree
    c) Neutral
    d) Disagree
    e) Strongly disagree
    f) Other (please specify)

15. Has your corporation implemented any pharma 4.0 elements in the R&D process? (Multiple selections possible)
    a) Lifecycle management
    b) Artificial intelligence
    c) Analytical Quality-by-Design (AQbD)
    d) Integration and traceability
    e) Advanced analytics
    f) Cloud-based data management
    g) Process Analytical Technology (PAT)
    h) Other (please specify)

16. Do you agree or disagree with the statement that the implementation of R&D innovative technologies in the pharmaceutical sector confers an advantage in a Covid-19 pandemic context?
    a) Strongly agree
    b) Agree
    c) Neutral
    d) Disagree

e) Strongly disagree
c) Other (please specify)
16.b Please elaborate, giving reasons for your answer where possible.

_____

17. How does R&D management take part in the implementation of new technologies application?

_____

18. What do you think will be the major challenge in the Pharmaceutical R&D area in the next ten years?
   a) Advances in technology
   b) Data integrity and cybersecurity
   c) Policy and regulatory activity
   d) Adequate return on innovation
   e) Digital therapeutics and personalized medicine
   f) Ethical issues and safety concerns

19. I would like to hear from you any additional information, thoughts or experience about R&D innovative technologies:

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