UNIVERSIDADE D
COIMBRA

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Relatório de Estágio e Monografia intitulada "Digital Transition in the Pharmaceutical Industry: the Impact in R&D and Supply Chain" referentes à Unidade Curricular "Estágio", sob a orientação do Dr. Carlos Pires e do Professor Doutor Sérgio Paulo Magalhães Simões, apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciências Farmacêuticas.

Outubro 2021

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Outubro de 2021

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Paulo Nuno da Costa Neves Barradas Rebelo

(Paulo Nuno da Costa Neves Barradas Rebelo)

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Parte I

Relatório de Estágio em Farmácia Comunitária

Farmácia Baeta Rebelo®

FARMÁCIA
BAETA REBELO
desde 1935

Sob orientação do Dr. Carlos Pires

Lista de Abreviaturas

MICF – Mestrado Integrado em Ciências Farmacêuticas

FFUC – Faculdade de Farmácia da Universidade de Coimbra

FC – Farmácia Comunitária

FBR – Farmácia Baeta Rebelo

SWOT – *Strengths, Weaknesses, Opportunities, Threats*

ANF – Associação Nacional das Farmácias

PIM – Preparação Individualizada da Medicação

PAD – Plano de Avaliação de Desempenho

RAM – Reação Adversa Medicamentosa

OF – Ordem dos Farmacêuticos

INFARMED, I.P – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

COVID-19 – Coronavirus Disease 2019

IF – Indicação Farmacêutica

ERASMUS – European Region Action Scheme for the Mobility of University Students (Plano de Ação da Comunidade Europeia para a Mobilidade de Estudantes Universitários)

1. Introdução

Após 4 anos e meio de formação teórica e prática, o plano de estudos do Mestrado Integrado em Ciências Farmacêuticas (MICF) da Faculdade de Farmácia da Universidade de Coimbra (FFUC) confere aos estudantes e futuros farmacêuticos a possibilidade de colocarem em prática as competências adquiridas, a fim de estas serem desenvolvidas na prática profissional. A realização de um estágio curricular de 810 horas dá integral cumprimento à diretiva do Parlamento Europeu, de 20 de novembro de 2013 que, para conclusão da formação, exige um mínimo de "quatro anos de formação teórica e prática a tempo inteiro..." juntamente com "seis meses de estágio em farmácia aberta ao público...".[1] Deste modo, a FFUC visa formar profissionais competentes, aptos a desempenhar um papel ativo na sociedade, na promoção da saúde e prevenção da doença.

A farmácia comunitária (FC) é um espaço caracterizado pela proximidade à população e pela acessibilidade ao medicamento e a serviços e cuidados de saúde diferenciados. Assim sendo, realizei o meu estágio curricular na Farmácia Baeta Rebelo (FBR), em Pedrógão Grande, sob orientação do Dr. Carlos Pires e colaboração por parte de toda a equipa.

Em agosto de 2020, tive a oportunidade de realizar um estágio de verão na mesma farmácia. Foi um mês que, apesar de curto, serviu de grande aprendizagem. Deste modo, sendo a FBR uma farmácia com elevada proximidade à comunidade local, revelou ser o local ideal para o desenvolvimento das minhas competências, tanto a nível profissional como pessoal. Posto isto, optei por dar continuidade ao processo iniciado.

Deste modo, o presente relatório visa retratar a minha experiência como estagiário na FBR, a partir de uma análise SWOT, onde identifico os pontos fortes e fracos, assim como as oportunidades e ameaças com as quais me fui deparando no decorrer do estágio. Ao longo da análise, irei também ilustrar a minha percepção do papel do farmacêutico comunitário na sociedade.

2. Farmácia Baeta Rebelo: Contextualização

A Farmácia Baeta Rebelo localiza-se no Largo da Devesa, na vila de Pedrógão Grande, distrito de Leiria, região centro de Portugal. O concelho de Pedrógão Grande tem actualmente 3392 habitantes[2], distribuídos por 3 freguesias – Pedrógão Grande, Graça e Vila Facaia. Desta população, aproximadamente 30% é população idosa (65 ou mais anos).[3]

Fundada a 4 de outubro de 1935, a FBR conta já com 86 anos de serviço à comunidade. Atualmente, é a única farmácia do concelho de Pedrógão Grande, sendo que ambas as freguesias de Graça e Vila Facaia têm o seu posto farmacêutico, dependente de uma farmácia do município de Figueiró dos Vinhos. Para além dos utentes do município, a FBR conta ainda com uma crescente população estrangeira residente em Portugal e com utentes dos munícipios limítrofes, como a Castanheira de Pêra, Góis, Pampilhosa da Serra, Sertã e Figueiró dos Vinhos.

A FBR funciona em regime de disponibilidade permanente, encontrando-se aberta 365 dias por ano e com acessibilidade a um farmacêutico de serviço fora do horário estipulado de abertura. Desta forma, é fortemente caracterizada pela proximidade à comunidade local e pelo acompanhamento regular dos seus utentes.

A equipa técnica da FBR é constituída por seis elementos: o proprietário e Diretor Técnico, Dr. Carlos Pires, três farmacêuticas, uma técnica auxiliar de farmácia e uma assistente operacional. De forma a promover a sua melhoria contínua, a FBR pertence à rede de farmácias Premium Farma, recebendo assessoria no reforço da comunicação digital, na consultoria financeira, de marketing e gestão de categorias.[4] É também associada da Associação Nacional das Farmácias (ANF).

São vários os serviços disponibilizados pela FBR, entre eles, os serviços farmacêuticos como, a determinação dos parâmetros bioquímicos e fisiológicos, a preparação de manipulados, a administração de vacinas e injetáveis e a preparação individualizada da medicação (PIM). Dispõe também de serviços subcontratados, como as consultas de nutrição, do pé diabético e podologia, e os rastreios auditivos.

Para além disso, a farmácia procura manter uma relação de proximidade com toda a comunidade, disponibilizando deslocações às freguesias limítrofes, de forma a prestar serviços, como a determinação dos parâmetros bioquímicos e fisiológicos ou as entregas de medicação a domicílios e instituições.

No dia 17 de junho de 2017, Pedrógão Grande foi o epicentro de um incêndio devastador, que causou inúmeros mortos e feridos. A FBR, em estreita relação com o centro de saúde, esteve desde o primeiro momento na frente de socorro às vítimas.[5] A população

ficou, desde então, marcada pelos incêndios, tendo a FBR reforçado a sua valorização perante os munícipes.

3. Análise SWOT

Neste capítulo, de forma a identificar os fatores fundamentais que contribuíram para o meu desenvolvimento enquanto estagiário e futuro profissional, irei utilizar a metodologia da análise SWOT - *Strengths, Weaknesses, Opportunities, Threats* (tabela 1). Deste modo, pretendo identificar por um lado, numa perspetiva interna, aqueles que foram para mim os pontos fortes e fracos intrínsecos à instituição, que maior impacto tiveram na minha aprendizagem. Por outro lado, num ponto de vista mais externo, as oportunidades e ameaças extrínsecas à instituição que foram sendo realçadas com o decorrer do estágio.

Tabela 1: Análise SWOT

Pontos Fortes	Pontos Fracos	Oportunidades	Ameaças
- Equipa técnica - Atendimento ao público - Autonomia na realização das tarefas - Integração no plano de avaliação de desempenho - Serviços farmacêuticos e acompanhamento farmacoterapêutico diferenciado	- Preparação de manipulados - Transição do Sifarma 2000® para novo módulo de atendimento do Sifarma®	- Participação nas entregas ao domicílio - Valorização generalizada do papel do farmacêutico por parte da população - Desenvolvimento de competências de comunicação em saúde - Atendimento por via telefónica - Dispensa de medicamentos hospitalares	- Distanciamento físico entre farmacêutico e utente - Ausência de formações presenciais no início do estágio

3.1. Pontos Fortes (*Strengths*)

3.1.1. Equipa técnica

Na minha opinião, a equipa técnica é um dos elementos mais diferenciadores numa farmácia. Afinal, são todos estes profissionais, desde os farmacêuticos aos técnicos auxiliares de farmácia que, com as suas diferentes funções, têm a responsabilidade de servir a população, promovendo o direito à saúde e bem-estar de cada cidadão. Desta forma, associado a este

sentido comum de missão, cada um dos elementos da equipa desempenha um papel fulcral no serviço prestado à população onde se insere.

Na FBR, encontrei uma equipa de profissionais exemplares (Anexo I), cuja alegria, competência e espírito de missão culminam num serviço ao próximo que inspira quem por lá passa. A equipa é constituída tanto por profissionais mais jovens, como por profissionais já com elevada experiência no ramo, resultando assim numa equipa dinâmica e heterogénea.

Ao iniciar o estágio, todos os colaboradores tiveram o cuidado de me integrar na equipa, de forma a sentir-me parte integrante da mesma. A organização da equipa é claramente um elemento de destaque, uma vez que os diferentes membros distribuíam funções e tarefas entre si, com vista à otimização dos processos e recursos. A comunicação efetiva entre todos os membros da equipa demonstrou também ser um fator preponderante tanto para o funcionamento da farmácia como para a minha evolução enquanto estagiário. Pessoalmente, foi um privilégio estar em constante contacto direto com o diretor técnico e proprietário da FBR, Dr. Carlos Pires. Tendo em conta a sua vasta experiência como farmacêutico comunitário e proprietário de farmácia, foi uma mais valia para o meu estágio ter a oportunidade de receber formação, tanto na vertente farmacêutica como na vertente de gestão.

3.1.2. Atendimento ao público

Tal como referido anteriormente, realizei o meu estágio de verão na FBR, onde tive oportunidade de desenvolver diversos processos relacionados com o *backoffice*. Essa experiência permitiu-me iniciar rapidamente e com alguma fluidez o atendimento ao público.

A FBR serve uma população alargada, tendo por isso bastante movimento, o que possibilitou que adquirisse maior confiança e incrementasse as minhas competências a nível do aconselhamento farmacêutico. Destaco ainda o facto de a farmácia servir uma população maioritariamente envelhecida, valorizando ainda mais o papel do farmacêutico comunitário. Uma vez que esta população, na sua grande maioria, implica maior atenção e cuidado por parte do farmacêutico, isso levou-me a ter uma maior atenção às suas necessidades. Durante os atendimentos procurei sempre ter uma escuta ativa, com a atenção focada nas necessidades do utente, de forma a poder fazer um atendimento competente, personalizado e humano.

3.1.3. Autonomia na realização das tarefas

Do início ao fim do estágio, houve sempre um grande incentivo por parte de toda a equipa para que ganhasse autonomia na realização das mais diversas tarefas. O facto de ter

sido o único estagiário fez com a equipa tivesse maior disponibilidade para me dar formação e me auxiliar sempre que necessário. Com o decorrer do estágio, através dos conhecimentos que fui adquirindo na prática profissional, a equipa foi-me delegando cada vez mais responsabilidade na execução autónoma de várias tarefas, abaixo descritas:

- atendimentos dos utentes;
- serviços farmacêuticos prestados no gabinete do utente (determinação dos parâmetros bioquímicos e fisiológicos);
- receção e respetiva organização dos produtos provenientes dos distribuidores, substituindo as tarefas da profissional responsável nas suas folgas;
- preparação da medicação para instituições, organização do receituário e respetiva faturação;
- preparação individualizada da medicação;
- entre outras.

3.1.4. Integração no plano de avaliação de desempenho (PAD)

Assim como os restantes membro da equipa, fui integrado no plano de avaliação de desempenho (PAD), que visa o alcance de objetivos por parte da equipa. Deste modo, ajudou-me a ter uma melhor compreensão das dinâmicas a nível da organização e gestão farmacêutica, assim como a desenvolver técnicas de venda, como *cross-selling* e *up-selling*, sempre com foco no utente e nas suas necessidades.

O PAD fez com que melhorasse vários aspetos relativamente ao atendimento e respetiva indicação farmacêutica. Foi desafiante para mim, uma vez que houve um maior esforço para aprofundar os meus conhecimentos relativamente a todos os produtos de saúde à venda na farmácia. Assim, adquiri a confiança necessária para melhor aconselhar o utente, de modo a satisfazer as suas necessidades e superar as suas expetativas e, em simultâneo, obter um retorno superior para a farmácia.

Desta forma, a equipa trabalhou sempre em conjunto, com vista ao alcance de metas comuns. O meu desempenho foi avaliado sempre com intenção de me tornar melhor profissional, mais atento às necessidades do utente e competente nas tarefas realizadas.

3.1.5. Serviços farmacêuticos e acompanhamento farmacoterapêutico diferenciado

Através da elevada proximidade à população, a FBR permite fazer o acompanhamento farmacoterapêutico de grande parte dos seus utentes, que sendo fidelizados, têm ficha aberta

na farmácia. A fidelização torna possível seguir a medicação que fazem, o é bastante relevante tanto no seguimento da adesão à terapêutica, como na identificação de possíveis reações adversas medicamentosas (RAM).

Para além disso, a FBR dispõe de serviços farmacêuticos que possibilitam um acompanhamento personalizado do utente, sendo estes:

- a determinação dos parâmetros bioquímicos e fisiológicos (medição da pressão arterial, do peso e altura, da glicémia e do colesterol total), permitindo a monitorização regular dos utentes. Este é um serviço recorrente no dia-a-dia da farmácia, o qual tive a oportunidade de prestar por diversas vezes, recomendando medidas não farmacológicas e farmacológicas ou reencaminhando para o centro de saúde, sempre que necessário;
- a preparação individualizada da medicação (PIM), cujo principal objetivo, de acordo com a Norma Geral da Ordem dos Farmacêuticos (OF), passa por "auxiliar o utente na correta administração dos medicamentos e promover uma melhor adesão à terapêutica." [6] (Anexo II)

Os farmacêuticos da FBR e os médicos do centro de saúde apresentam uma estreita relação de colaboração e entreajuda, com foco na saúde e bem-estar do utente. Esta proximidade deve-se ao facto de ambos estarem inseridos na vila de Pedrógão Grande, o que facilita a comunicação. Sendo assim, sempre que há necessidade de esclarecimentos, o farmacêutico contacta diretamente o médico, e vice-versa.

3.2. Pontos Fracos (*Weaknesses*)

3.2.1. Preparação de manipulados

De acordo com o INFARMED,I.P. - autoridade reguladora do medicamento em Portugal, considera-se medicamento manipulado "qualquer preparado oficinal ou fórmula magistral preparado e dispensado sob a responsabilidade de um farmacêutico**",** que certifica a sua qualidade e segurança.[7] Estes medicamentos são receitados pelo médico quando o utente necessita de um tratamento mais personalizado, exigindo uma forma farmacêutica ou dosagem que não exista no mercado.

Tal como supramencionado, a FBR é uma farmácia com bastante movimento e, portanto, com bastante atividade ao balcão, sendo cada elemento da equipa destacado para tarefas específicas. Tendo sido o atendimento ao balcão um dos pontos fortes do meu estágio, a preparação de medicamentos manipulados acabou por não ser um ponto central do mesmo. Para além disso, com o aumento do número de opções terapêuticas, sinto que a prescrição

médica e a preparação destes medicamentos na FC tem vindo a diminuir, sendo estes maioritariamente adquiridos a farmácias especializadas.

Ainda assim, foi-me dada a oportunidade de auxiliar a farmacêutica responsável na preparação de uma **vaselina salicilada 5%** e também, sempre que possível, observar a preparação dos mesmos. Foram ainda explicados os cálculos necessários para obter o preço final do manipulado. (Anexo III)

3.2.2. Transição do Sifarma 2000® para novo módulo de atendimento do Sifarma®

No estágio de verão que realizei na FBR, esta ainda utilizava o sistema informático Sifarma 2000®. Porém, quando iniciei o estágio curricular, a farmácia encontrava-se já a utilizar o novo módulo de atendimento, recorrendo ainda ao Sifarma 2000® para aceder a algumas funcionalidades.

Tendo em conta o avanço tecnológico deste tipo de *softwares*, o Sifarma 2000® apresentava-se, de facto, bastante desatualizado em termos de intuição e a nível gráfico. No entanto, este foi evoluindo ao longo do tempo, adaptando as suas funcionalidades às necessidades do farmacêutico. Uma vez que os sistemas ainda se encontravam numa fase de transição, o novo módulo de atendimento chegou incompleto às farmácias, sem todas as funcionalidades necessárias ao dia-a-dia do farmacêutico, sendo necessário usar ambos os sistemas em algumas tarefas.

Desta forma, numa fase inicial tive alguma dificuldade no atendimento, pois não era possível transferir o histórico do utente armazenado no Sifarma 2000® para o novo módulo de atendimento, limitando assim o acesso à ficha do utente. Este ponto era fulcral na maioria dos atendimentos, uma vez que, tal como mencionado anteriormente, grande parte dos utentes são fidelizados, sendo importante aceder ao historial para melhor os servir. Consequentemente, foi muitas vezes necessário utilizar os dois sistemas em simultâneo, o que causou alguns constrangimentos na fluidez do atendimento.

3.3. Oportunidades (*Opportunities*)

3.3.1. Participação nas entregas ao domicílio

Durante o estágio foi-me dada a oportunidade de fazer entregas ao domicílio a utentes que não tinham possibilidade de se deslocar à farmácia. (Anexo IV) Na FBR, as entregas ao domicílio já eram prática habitual antes da pandemia da Covid-19, sendo reforçadas com a mesma. Demonstrou ser relevante, uma vez que, muitos utentes não tinham capacidade de se

deslocar à farmácia devido a constrangimentos a nível de saúde, ou de mobilidade. É uma atividade diferenciadora na profissão farmacêutica, focada inteiramente no bem-estar do utente. Desta forma, a distância ou incapacidade do utente não se tornam impeditivos ao usufruto de um serviço personalizado de grande qualidade.

3.3.2. Valorização generalizada do papel do farmacêutico por parte da população

Um dos motivos que influenciou a minha escolha em estagiar na FBR foi o facto de esta ser uma farmácia muito próxima da população, permitindo um melhor acompanhamento do utente. De um modo geral, notava-se uma grande confiança da população nos profissionais da farmácia.

Hoje em dia, o profissionalismo e competência do farmacêutico torna-se cada vez mais importante, tendo em conta a facilidade de acesso a informação pouco fundamentada, podendo originar desinformação. Os utentes da FBR confiam no aconselhamento do farmacêutico, considerando que a farmácia é o local indicado para a obtenção de informação de qualidade.

Ainda assim, a mudança paradigmática da profissão farmacêutica, devido às novas tecnologias e consequente *bypass* ao atendimento tradicional, leva a que o farmacêutico sinta a necessidade de explorar novas vias de comunicação e de aproximação ao utente. A FBR não é exceção, dando uso a plataformas digitais, como o *Instagram* e *Facebook*, de forma a promover serviços e campanhas, assim como a desenvolver material multimédia de educação para a saúde. Foi-me dada a oportunidade de realizar um vídeo[8] para as redes sociais da FBR no âmbito do Dia Mundial das Doenças Raras (28 de Fevereiro), com o objetivo de consciencializar a população sobre esta temática. (Anexo V) O vídeo esteve também em exposição na televisão da farmácia, juntamente com outros vídeos de educação para a saúde.

Deste modo, não só senti que os utentes da FBR valorizam bastante o papel do farmacêutico, como pude observar o esforço diário de cada um dos farmacêuticos para manter um papel ativo na comunidade.

3.3.3. Desenvolvimento de competências de comunicação em saúde

A crise pandémica veio reforçar a importância do papel do farmacêutico comunitário e respetiva farmácia na educação para a saúde. Desta forma, citando as palavras da atual presidente da ANF, Dra. Ema Paulino, considerando que "as farmácias são a porta de entrada no sistema de saúde" é evidenciado o seu importante papel na promoção da saúde pública.[9]

Tendo em conta as circunstâncias durante o meu estágio, destaco o dever de sensibilizar os utentes para a vacinação.

O estágio colocou-me à prova tanto a nível profissional como a nível social. Desenvolvi capacidades de comunicação e de educação para a saúde, o que revelou ser fundamental na relação com o utente e na confiança transmitida no aconselhamento. Foi um processo de aprendizagem notório, que permitiu a minha melhoria contínua na promoção da saúde, prevenção da doença e hábitos de vida saudável com máxima eficácia. A competência e profissionalismo de toda a equipa fez com que procurasse aprofundar mais os meus conhecimentos, de forma a poder esclarecer o utente de todas as suas dúvidas. Para além disso, sempre que necessário solicitei apoio por parte da equipa.

3.3.4. Atendimento por via telefónica

A pandemia exigiu uma adaptação a vários níveis por parte das farmácias. Destaco aqui a oportunidade que esta realçou do atendimento por via telefónica. Demonstrou ser desafiante pelo facto de não estarmos presencialmente com o utente, tendo apenas o canal auditivo para prestar atenção às suas necessidades. A sua relevância deveu-se aos motivos atrás mencionados, pelos constrangimentos de mobilidade por parte da população, especialmente nos primeiros meses de estágio, quando a população teve de iniciar um novo confinamento.

3.3.5. Dispensa de medicamentos hospitalares

No seguimento do ponto anterior, outra oportunidade que surgiu resultante da pandemia da Covid-19 foi a possibilidade de dispensar medicamentos hospitalares em FC, procedimento este, previamente realizado exclusivamente em farmácias hospitalares.

Os utentes de medicação hospitalar em regime de ambulatório, como é o caso dos utentes transplantados, com cancro, e outras doenças incapacitantes são muitas vezes utentes imunodeprimidos, sendo a infeção por Covid-19 um risco acrescido para eles. Assim, de forma a salvaguardar a saúde destes utentes, no dia 4 de abril de 2020, foi emitido um Despacho pela Ministra da Saúde, que determinou "medidas de caráter excecional [...] de fornecimento de medicamentos dispensados por farmácia hospitalar em regime de ambulatório, [...] através da dispensa em farmácia comunitária".[10] Deste modo, as farmácias comunitárias começaram a prestar este serviço à população, sendo esse o caso da FBR.

Esta medida, veio aliviar estes utentes, que muitas vezes tinham de percorrer longas distâncias para levantar a medicação no hospital. Deste modo, tive a oportunidade de

contactar com medicamentos hospitalares, como o Fingolimod, terapêutica em doentes com esclerose múltipla, e o Tacrolimus, medicamento utilizado na profilaxia da rejeição de transplante. Para além disso, procedi ao registo da dispensa e fiz o acompanhamento do possível agravamento da doença e RAM, sob supervisão de um farmacêutico.

3.4. Ameaças (*Threats*)

3.4.1. Distanciamento físico entre farmacêutico e utente

Durante a pandemia as farmácias mantiveram-se sempre em funcionamento e, portanto, foram sempre as primeiras a dar o exemplo, cumprindo todas as medidas de prevenção e segurança, de forma a salvaguardar tanto os profissionais como os utentes. No entanto, ao longo do estágio, fui sentindo que as máscaras, acrílicos e o distanciamento físico entre farmacêutico e utente, contribuíram em alguns momentos para uma certa despersonalização do farmacêutico e do respetivo atendimento. O ser humano utiliza diversas formas de comunicação, de expressão e de criação de empatia. Assim, a dificuldade de observação das expressões faciais e da audição ao longo de alguns atendimentos, constituiu no meu ponto de vista, uma ameaça ao serviço farmacêutico prestado.

3.4.2. Ausência de formações presenciais no início do estágio

Uma das principais responsabilidades do farmacêutico passa pela sua formação contínua, de forma a manter-se atualizado e aumentar o seu leque de competências. Sendo este um promotor da saúde pública e especialista na área do medicamento, deve manter-se atualizado nas mais diversas áreas, principalmente nas que se relacionam com o uso dos medicamentos e produtos farmacêuticos e respetivos efeitos. Assim, o farmacêutico comunitário deve dominar as características de todos os produtos à disposição na farmácia, de modo a prestar um serviço de máxima qualidade.

Deste modo, tendo o meu estágio sido iniciado em janeiro, perto da data em que se iniciou o novo confinamento, a maioria das marcas suspenderam as formações presenciais, para salvaguardar todos os intervenientes. Estando numa fase inicial do estágio e, com algum desconhecimento de características mais específicas de alguns dos produtos, senti falta de formação por parte das marcas. Numa fase inicial, tanto as marcas como as farmácias encontravam-se em fase de readaptação, sendo que mais tarde iniciaram formações online, às quais pude assistir, como foi o caso das formações da Bayer®, da Patta®, e da Uriach® e, também algumas formações presencias, da Arkopharma® e da Fresenius-kabi®. Estas formações

colmataram assim essa minha necessidade, proporcionando-me maior confiança no aconselhamento.

De qualquer forma, como já referi anteriormente, sempre que precisei tive bastante recetividade e disponibilidade por parte de todos os elementos da equipa para me dar formação e todo o apoio necessário.

4. Casos Práticos

4.1. Caso A

A.G., utente do sexo masculino, com 63 anos, dirige-se à Farmácia referindo queixas de obstipação crónica, agravada nos últimos dias, com distensão e desconforto abdominal. Refere habitualmente controlar através do reforço de legumes verdes na alimentação e fruta. Contudo, não tem sentido melhoria com estas medidas, pelo que solicita um produto laxante para alívio de sintomas. Averiguados hábitos de vida, constato que ultimamente tem saído pouco de casa, uma vez que com o aproximar dos dias quentes de verão, não tem conseguido fazer as suas habituais caminhadas. Questionados sinais de alarme, nomeadamente perda de peso recente ou perda de sangue nas fezes, refere que não notou qualquer um destes.

Indicação Farmacêutica (IF): Nesta situação, como medidas farmacológicas comecei por indicar um produto laxante, Dulcosoft® pó para solução oral, cujo princípio ativo é macrogol 4000, com efeito osmótico no cólon, retendo água no lúmen intestinal e amolecendo dessa forma as fezes. Expliquei que podia dissolver uma a duas saquetas em água e beber, preferencialmente pela manhã, de forma regular durante pelo menos duas semanas. Adicionalmente, para alívio simultâneo das queixas de distensão abdominal e flatulência, sugeri a toma de Aero-OM® 42mg comprimidos mastigáveis, cujo princípio ativo é simeticone, com efeito na redução da acumulação de gases no intestino, devendo mastigar 2 comprimidos após as refeições, até quatro vezes por dia. Adicionalmente, recomendei um probiótico à base de lactobacilos, com efeito benéfico na regularização da flora intestinal e consequentemente do trânsito intestinal.

Como medidas não farmacológicas, reforcei o aumento da ingestão de água. Esta é uma medida de extrema importância, por um lado, como adjuvante necessário para o efeito de um laxante osmótico, por outro, porque nos estávamos a aproximar do verão, com habitações habitualmente mal isoladas e quentes. A desidratação é comum, sobretudo nos indivíduos mais velhos, o que poderia ter sido o motivo do agravamento recente da sua obstipação crónica. Paralelamente, reforcei a importância de uma dieta com reforço de fibras não solúveis, nomeadamente legumes de folha verde escura, frutas com casca, frutos como

kiwi, manga, papaia que promovem o trânsito intestinal. Incentivei ao retorno das suas caminhadas diárias, procurando as alturas mais frescas do dia. Referi por último que caso não melhorasse com estas medidas, deveria consultar o seu médico, para avaliação de outras causas de obstipação.

4.2. Caso B

C.T., utente do sexo feminino, com cerca de 80 anos, dirige-se à Farmácia com queixas de irritação do couro cabeludo. Apresentava uma receita médica da consulta de Dermatologia em nome da sua neta, na qual constava KPL champô e Nizoral (cetoconazol) utilizados no tratamento da dermatite seborreica do couro cabeludo, dizendo que devia ter o mesmo problema.

IF: Pedi para observar o couro cabeludo da senhora, e constatei a utilização de tinta para o cabelo, e ausência de descamação ou sinais de inflamação do couro cabeludo, pelo que indiquei que deveria evitar a utilização de tinta para o cabelo e recomendei um champô calmante, Klorane Peónia.

Este caso foi um exemplo do papel do farmacêutico na educação para a saúde e controlo da automedicação.

4.3. Caso C

M.J., utente do sexo feminino, com cerca de 55 anos, dirige-se à Farmácia para adquirir a sua medicação habitual, com exceção da rosuvastatina prescrita. Questionei o motivo de não levar a estatina habitual, ao que a utente refere que tinha deixado de tomar há cerca de dois meses, após ter visto num programa de televisão um especialista referir que esta tinha efeitos secundários significativos, pelo que decidiu suspender este fármaco, porque já tinha sentido algumas dores nas pernas.

IF: Perante esta situação sugeri realizar uma avaliação do colesterol total, para confirmar se não teria havido alteração significativa dos valores com a suspensão da estatina. Apesar da avaliação do colesterol total não ser isoladamente um indicador fidedigno na avaliação de dislipidémia, uma vez que não permite inferir os valores de LDL (indicador de risco cardiovascular), dá informação relevante do controlo metabólico, sobretudo em comparação com anteriores valores sob terapêutica. Constatei que o valor de colesterol total da utente se encontrava acima dos valores de referência (<190mg/dL), e acima do padrão habitual da utente. Esclareci a utente que a suspensão da medicação estava a ter impacto nefasto nos seus níveis de colesterol, com riscos importantes para a sua saúde, aumentando o risco cardiovascular. Confirmei que a classe de fármacos, como qualquer outra, não é desprovida de efeitos secundários, mas esclareci que os benefícios suplantam os riscos, e que no caso de

dúvidas quanto à sua medicação deve sempre esclarecer junto do seu farmacêutico ou médico antes de tomar alguma decisão.

5. Considerações finais

O estágio curricular em FC foi, para mim, o culminar dos 5 anos de curso do MICF. Abriu-me as portas para o mercado de trabalho, de modo a educar-me para a realidade e desafios com que os farmacêuticos se deparam diariamente. Desta forma, colocou-me à prova, testando não só os meus conhecimentos técnico-científicos adquiridos ao longo do curso, como também as mais diversas competências sociais e emocionais, essenciais à prática farmacêutica.

Esta etapa foi imprescindível para o meu percurso académico, pois preparou-me para uma realidade profissional que desconhecia. Após realizar 810 horas de estágio na FBR, sinto-me hoje mais capaz de aplicar as minhas competências, de modo a corresponder às necessidades que o mundo profissional exige. Para além disso, ao vivenciar em primeira mão o dia-a-dia de uma FC, pude compreender a elevada responsabilidade e impacto que o farmacêutico comunitário tem na comunidade que serve, com foco constante na promoção da saúde pública.

O plano curricular do MICF é bastante abrangente, percorrendo todo o vasto ciclo do medicamento. Desta forma, está delineado no sentido de abordar diferentes conceitos de uma forma transversal, com foco na integração e consolidação dos mesmos. Na vertente de FC, destaco a cadeira de 5º ano de "Indicação Farmacêutica" que, na minha perspetiva, prepara bem o estudante para a prática profissional, promovendo o correto aconselhamento ao utente e respetiva IF, relacionando os conceitos técnico-científicos lecionados ao longo do curso. No entanto, no 4º ano não tive a oportunidade de fazer a cadeira de "Organização e Gestão Farmacêutica" na FFUC, tendo obtido equivalência através da cadeira "Business economy of pharmaceutical industry", realizada ao abrigo do programa ERASMUS. Provavelmente por essa razão, senti alguma falta de noções de gestão no âmbito da FC, que, do meu ponto de vcumista, é uma área de extrema relevância para o farmacêutico comunitário.

Resta-me referir que foi um privilégio realizar o meu estágio curricular na FBR, contribuir para os seus 86 anos de história e, principalmente, fazer parte de uma equipa que tanto contribuiu para o meu crescimento, a todos os níveis. Agradeço, deste modo, ao Dr. Carlos, à Dra. Sofia, à Dra. Maria João, à Dra. Beatriz, à Rita, à Fátima e à Dª. Helena, por toda a paciência, confiança e, acima de tudo, por me ensinarem a ser um profissional mais competente e um ser humano mais íntegro.

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7. Anexos

7.1. Anexo I

A equipa da Farmácia Baeta Rebelo:

Figura 1: Dª. Helena, Fátima, Dr. Carlos, Rita, Dra. Beatriz, Dra. Maria João, Dra. Sofia, Eu

7.2. Anexo II

Preparação Individualizada da Medicação (PIM) de utente para duas semanas:

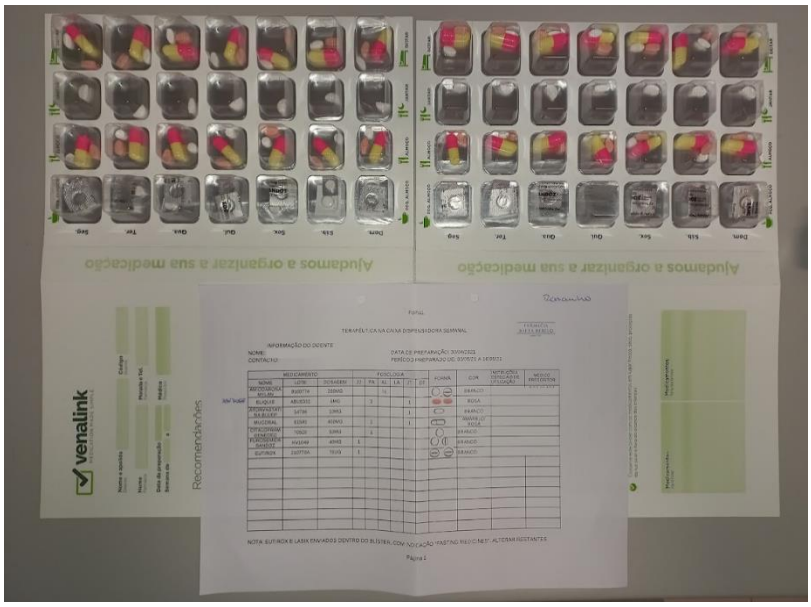

Figura 2: Preparação Individualizada da Medicação (PIM); Fotografia tirada por mim

7.3. Anexo III

Exemplo dos cálculos para obtenção do preço da vaselina salicilada:

Cálculo do preço de venda

Matérias - Primas:

Materias Primas	Embalagem existente em armazem		Preço de aquisiçaõ de uma dada quant.unit.(s/iva)		Quantidade	factor	Preço da Matéria Prima
	Quantidade adquirida(g/ml)	Preço de aquisição(s/iva)	Quantidade unitária (g/ml)	preço	a usar	multiplicativo	utilizada na preparação
Ácido Salicílico	50	5,71 €	1	0,1142	4 g	2,2	1,00 €
Vaselina Sólida	1000	7,05 €	1	0,0071	26 dc	1,9	0,35 €
				#DIV/0!		#N/A	#DIV/0!
				#DIV/0!		#N/A	#DIV/0!
				#DIV/0!		#N/A	#DIV/0!
				#DIV/0!		#N/A	#DIV/0!
						Subtotal A	1,35 €

Honorários de Manipulação:

	Forma Farmacêutica	Quantidade (g/ml)	F(€)	Factor Multiplicativo	Valor
Valor referente à quantidade base	solução	30	5,05 €	3	15,15 €
Valor adicional			5,05 €	0,005	0,00 €
	Quantidade Total Manipulado	30		Subtotal B	15,15 €

Material de Embalagem:

Material de Embalagem	Preço de aquisição (s/IVA)	Quantidade	Factor Multiplicativo	Valor
Recipiente Unguator 30	0,7	1	1,2	0,84 €
				0,00 €
			Subtotal B	0,84 €

PREÇO DE VENDA AO PÚBLICO DO MEDICAMENTO MANIPULADO:	(A+B+C)X1,3	22,55 €
	IVA	1,35 €
	D	23,90 €

Dispositivos Auxiliares de Administração:

Dispositivos	Preço unitário	Quantidade	Valor
			0,00 €
		E	0,00 €
		PREÇO FINAL: D+ E	23,90 €

OPERADOR: _____ SUPERVISOR: _____

ATD-IMP-10-01

Rubrica do Director Técnico	Data

Figura 3:Exemplar da folha de cálculo para obtenção de preço da vaselina salicilada

7.4. Anexo IV

Entrega ao domicílio realizada por mim:

Figura 4: Entrega ao domicílio; Fotografia tirada por mim

7.5. Anexo V

Imagens do vídeo realizado para as redes sociais da FBR, no âmbito do Dia Mundial das Doenças Raras (28 de fevereiro):

Figura 5: 6 imagens do vídeo de consciencialização sobre doenças raras; Realizado por mim

Parte II

Monografia

Digital Transition in the Pharmaceutical Industry: the Impact in R&D and Supply Chain

Sob orientação do Professor Doutor Sérgio Paulo Magalhães Simões

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Abstract

Throughout time, the pharmaceutical industry has gone through multiple challenging circumstances and has consistently proven to be capable of adapting and prospering from them. Currently, the industry is going through substantial scientific and technological breakthroughs occurring at various stages of the medicine's life cycle.

The aim of this dissertation is to discuss the main driving forces behind the ongoing digital revolution occurring in the pharmaceutical industry. The main topics of discussion will be regarding the impact of artificial intelligence (AI) across different stages of drug discovery and development, as well as the prospects of blockchain technology and e-commerce in the pharmaceutical supply chain.

Although there have been several scientific advances over the last years, the overall process of research and development (R&D) remains very lengthy and costly, with an extremely high failure rate. Therefore, multiple companies, particularly AI-based startups, are developing and applying models to optimize inefficient processes within the whole drug development cycle.

In the supply chain, stakeholders are also exploring the use of digital technologies to address common issues. These comprise the lack of trust, transparency, and traceability between stakeholders. Thus, research on the use of blockchain technology is being conducted to address those challenges. The technology is prospected to monitor supply chains securely and transparently, optimizing workflows and reducing operational costs, human mistakes, and fraudulent practices.

In order to cope with the demands of this digital transition, pharmaceutical companies will need to invest in IT expertise and find a strategy to overcome their strictly regulated and non-integrated environment.

Keywords: Research and Development, Artificial Intelligence, Supply Chain, Blockchain, Pharma4.0

Resumo

A indústria farmacêutica tem vindo a enfrentar inúmeros desafios ao longo do tempo, tendo sempre demonstrado capacidade de se adaptar e desenvolver. Atualmente, a indústria está a atravessar uma fase de profunda transformação científica e tecnológica ao longo das diferentes fases do ciclo de vida do medicamento.

Ao longo desta dissertação vão ser discutidas as principais forças impulsionadoras da atual revolução digital na indústria farmacêutica. Os principais tópicos de discussão serão em torno do impacto da inteligência artificial (IA) nas diferentes fases de investigação e desenvolvimento de novos fármacos, assim como as perspetivas do *blockchain* e do *e-commerce* nas cadeias de distribuição farmacêutica.

Apesar de terem ocorrido vários avanços científicos ao longo dos anos, a investigação e desenvolvimento (I&D) de fármacos continua a ser um processo longo e dispendioso, com uma taxa de insucesso extremamente elevada. Deste modo, várias empresas, particularmente as startups de IA, encontram-se a desenvolver e a implementar modelos que visam a otimização de processos ao longo do desenvolvimento de fármacos.

Nas cadeias de distribuição farmacêutica também estão a ser exploradas diferentes tecnologias digitais para fazer face aos problemas atuais. Alguns destes problemas estão relacionados com a falta de confiança e transparência entre os intervenientes. Assim, de forma a enfrentar estes desafios encontram-se atualmente em desenvolvimento diferentes estudos relativamente à aplicabilidade da tecnologia *blockchain*. Esta tecnologia visa monitorizar as cadeias de distribuição de forma segura e transparente, com o intuito de otimizar processos e minimizar custos operacionais, o erro humano, e práticas fraudulentas.

De modo a fazer face às exigências desta transição digital, as empresas farmacêuticas terão de investir em recursos humanos com competências em tecnologias de informação, e encontrar estratégias para ultrapassar o apertado enquadramento regulamentar.

Palavras-chave: Investigação e Desenvolvimento, Inteligência Artificial, Cadeias de Distribuição, Blockchain, Farma4.0

List of Abbreviations

3D – Three Dimensional

3D-CNN – Three Dimensional Convolutional Neural Network

3PL – Third-Party Logistics

AI – Artificial Intelligence

ALS – Amyotrophic Lateral Sclerosis

AAK1 – AP2-associated protein kinase 1

API – Active Pharmaceutical Ingredient

CAGR – Compound Annual Growth Rate

CIM – Computer-Integrated Manufacturing

D – Discriminator

DDRI – Discoidin Domain Receptor 1

DL – Deep learning

DLSF – Deep Learning-Based Scoring Functions

DSCSA – Drug Supply Chain Security Act

EFPIA – European Federation of Pharmaceutical Industries and Associations

EMVO – European Medicines Verification Organization

EUIPO – European Union Intellectual Property Office

FDA – Food and Drug Administration

FMD – Falsified Medicines Directive

G – Generator

GAN – Generative Adversarial Networks

GCN – Graph Convolutional Network

GDP – Good Distribution Practices

GENTRL – Generative Tensorial Reinforcement Learning

GTIN – Global Trade Identification Number

EHR – Electronic Health Records

HTS – High Throughput Screening

IATA – International Air Transport Association

ICH – International Council of Harmonization of Technical Requirements for Pharmaceuticals for Human Use

IoT – Internet of Things

ISPE – International Society of Pharmaceutical Engineering

IT – Information Technology

LBVS – Ligand-based Virtual Screening

MDD – Multi-Dose Drug Dispensing

MDS-UPDRS – Movement Disorder Society-Unified Parkinson's Disease Rating Scale

ML – Machine Learning

NME – New Molecular Entity

OECD – Organization for Economic Co-operation and Development

PD – Parkinson's Disease

PQS – Pharmaceutical Quality System

PwC – PricewaterhouseCoopers

QSAR – Quantitative Structure-Activity Relationship

R&D – Research and development

RBPs – RNA-Binding Proteins

RL – Reinforcement Learning

RWD – Real World Data

RWE – Real World Evidence

SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

SBVS – Structure-based Virtual Screening

SCM – Supply Chain Management

U.S. – United States of America

VS – Virtual Screening

WHO – World Health Organization

XRC - X-ray Crystalography

1. Introduction

Since the foundation of the pharmaceutical industry in the 19th century, health and social crisis were usually substantial opportunities for its development. The need for developing medicines to treat wounded soldiers in war, as well as vaccines to solve global pandemics, further propelled the industry, contributing to the progress of healthcare. Therefore, throughout time, pharmaceutical companies have always shown great flexibility to adapt to a wide range of circumstances and prosper from them, as we are witnessing today.[1]

The research and development (R&D) of novel medicines is the ultimate goal for the pharmaceutical sector, providing steady growth for companies by largely contributing to their income. Top pharmaceutical companies usually designate an average of 20 percent of their total revenue to invest in R&D.[2] However, as the innovators' patents achieve their expiration date, the competition from generic companies follows. As a result, the cost of medicines for payers decreases. Thus, on the one hand, democratizing its access, while on the other hand leading to a significant impact on the revenue of innovators.

The pharmaceutical industry is a vast network of companies. The key players can be summarized from big pharma to biotechnology startups, generics companies, and suppliers. These players are highly dependent on each other. Therefore, much of the innovation occurs outside big pharma's labs as well as the investment in drug development, which costs have been escalating quickly. For this reason, in the last years, one of the central business strategies for big pharma has relied on mergers and acquisitions or collaborations between them, research-intensive startups, and suppliers. Usually, big pharma companies reach out for drugs in late-stage clinical trials and innovative technological capabilities regarding research and development, diagnostics, and real-world data sources. These collaborations are often compelling for startups, leading them to expand their business worldwide by having access to new commercial channels and know-how.[3]

Currently, the leading pharmaceutical markets are based in the United States of America (U.S.), Japan, and Europe. In 2018, the global pharmaceutical market reached around 1.2 trillion dollars and is expected to achieve 1.5 trillion dollars by 2023.[4] Data from 2019 show that North America accounted for 48.7% of the world's pharmaceutical sales compared with 22,9% in Europe. When it comes to global sales of innovative medicines launched from 2014 to 2019, 62.3% were on the U.S. market, accounting for a considerable difference when compared to 18.4% on the European market.[5]

The accelerated market growth and research in emerging economies like China, India and Brazil is gradually leading to a market shift from Europe to these countries. According to

the IQVIA Institute, from 2014 to 2019, the Brazilian, Indian, and Chinese markets have respectively increased at a Compound Annual Growth Rate (CAGR) of 11.2%, 11.1%, and 6.9%, while the top five European Union markets had an annual growth of 5.4%, and the U.S. of 6.1%.[4]

The Pharmaceutical industry is at the beginning of a new era, with ongoing scientific and technological advances occurring in different stages of the medicine's life cycle. The evolving shift to personalized therapies and the unlimited potential offered by Information Technology (IT) are currently among the top strategic priorities for pharmaceutical companies.

Therefore, the main scope of this dissertation will be concerning the impact and expectations of the digital transformation both in terms of the research and development of novel drugs as well as in the pharmaceutical supply chain. However, before moving forward to the main topics, it is crucial to understand some of the driving forces behind industrial digitalization. Accordingly, the concepts of Industry 4.0, Pharma 4.0, and Artificial Intelligence will be summarized in the next chapter.

2. Industry 4.0

Since the emerging of the First Industrial Revolution in the late 18th century, the global industry has evolved through three distinct industrial revolutions. The fourth is currently underway, thus still in its early stages. Figure 1 gives a brief description of the key elements of each industrial revolution.[6]

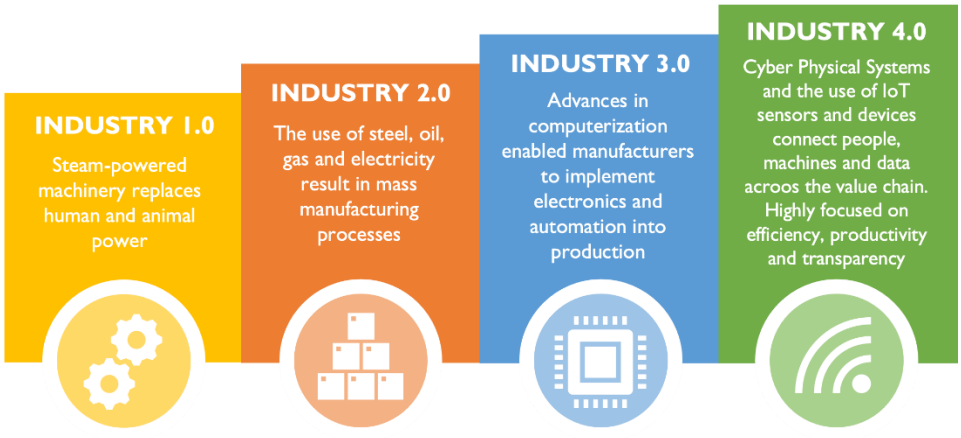

Figure 1: From steam to sensors: Industrial revolutions. [126]

The Fourth Industrial Revolution began occurring in the last decades. In 2011, the German government introduced the term "Industry 4.0", which referred to the integration of

emerging digital technologies in different steps of the industrial value chain.[6] However, currently most industries use computer-integrated manufacturing (CIM) models, where the manufacturing systems run independently. As a result, the programmed routines lack flexibility, incapable of evolving over time unless externally modified by humans. In contrast, within the Industry 4.0 framework, manual work is replaced by fully automated assembly lines, autonomous robots, and algorithms. Thus, leading to the transformation of conventional companies into a lot more flexible, data-driven, intelligent, and networked ones.[7] Particularly, in the supply chains, the impact is determined by opportunities regarding digital traceability of individual goods and automation of logistics processes, with expectations to further protect customers, maximize economic gains and reduce the environmental impact.

Essentially characterized by digitalization, automation and connectivity through the entire value chain, it comprises different technologies, such as the ones described in figure 2.

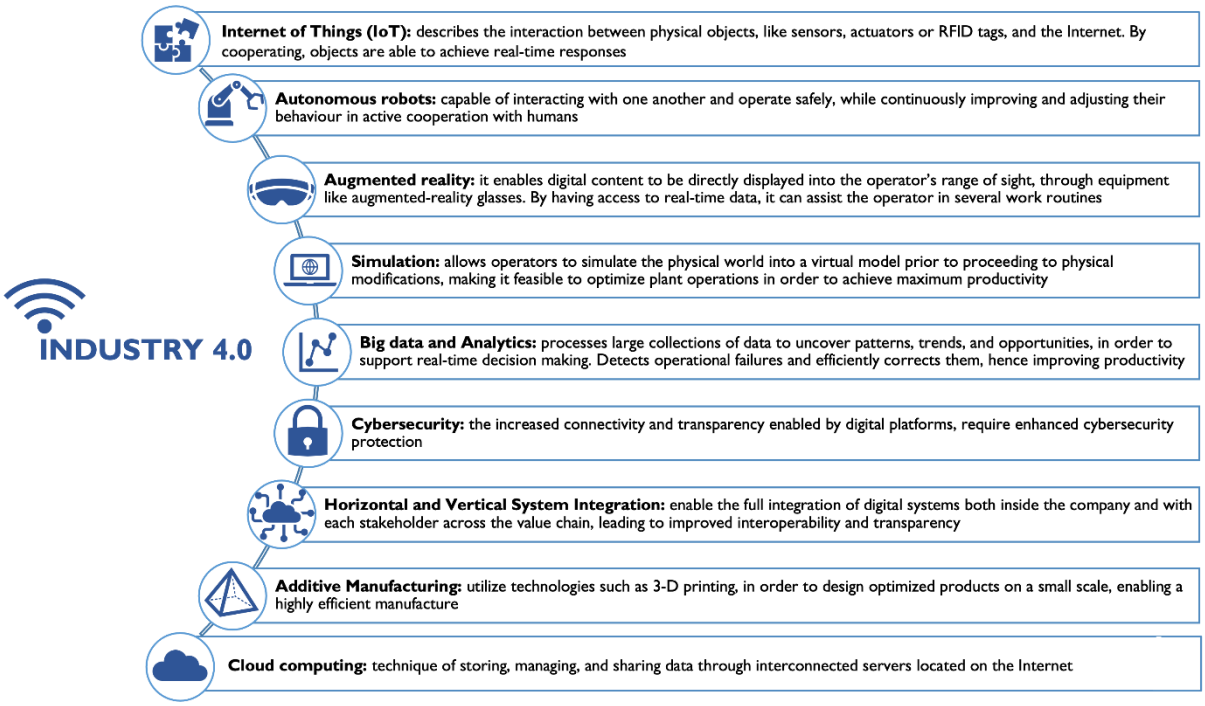

Figure 2: Most relevant technologies transforming Industry 4.0. [79]

In 2015, PricewaterhouseCoopers (PwC) conducted a study surveying 2100 executive members of industrial companies from 26 countries. By this time, 72% of global executive members were expecting that in 2020 their companies would achieve high levels of digitalization. Taking Portugal as an example, 57% of the companies surveyed anticipated an average revenue growth of 10%. Moreover, 55% expected cost savings of more than 10%, and 70% predicted over 10% efficiency rise.[8]

However, the study also highlighted several challenges regarding Industry 4.0 adoption. Although there are high expectations for the rise in revenue, cost savings and efficiency, the implementation of Industry 4.0 processes and technologies will undoubtedly take a lot of time and effort. The major challenge identified was regarding the lack of digital culture and skills to deal with this transition. Therefore, in order to quickly adapt to new processes and technologies, everyone involved in Industry 4.0 processes must be highly qualified and constantly up-to-date.[8]

2.1. Pharma 4.0

When it comes to the pharmaceutical sector, the International Society of Pharmaceutical Engineering (ISPE) came up with the concept "Pharma 4.0" in order to assist the pharmaceutical industry in overcoming challenges imposed by new technologies.[9]

Thus, to apply the Industry 4.0 metrics to the strictly regulated pharmaceutical industry, an operating model using the principles of ICH Q10 Pharmaceutical Quality System (PQS)[10] has been developed. The guideline outlines critical elements and enablers from a pharmaceutical and regulatory viewpoint across the product's life cycle and value chain. As the figure 3 illustrates, the Pharma 4.0 operating model consists of four elements and two enablers, that are described below.[11]

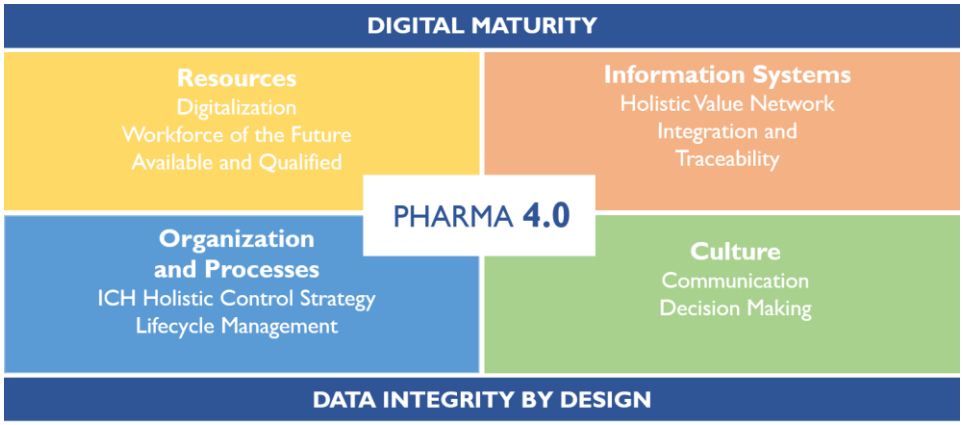

Figure 3: Pharma 4.0 Operating Model. Adapted from [13]

Elements:

i) **Resources:** comprise physical assets (human resources, equipment, machinery, materials, and the final product) and the way they interact with each other;

ii) **Organization and Processes**: refers to the structural organization of the company and its processes. A fully agile company could be created by establishing self-organized teams, without silos, that are accountable for their product or task from beginning to end;

iii) **Information Systems:** companies must establish a company-wide and value-chain-wide data framework by organizing, processing, storing, and transferring data. Thus, access to high-quality data is a crucial success factor to product's lifecycle decisions throughout product development, production, quality, supply chain, and business; [12]

iv) **Culture:** refers to the company's structure, whereby the culture must be completely aligned between the different departments, resulting in mutual agreement and a shared knowledge base. Developing an organizational culture of transparency and trust is critical for the execution of a holistic control approach.[12]

Enablers:

i) **Digital Maturity:** the main catalyst for the organization's shift to a data-driven, agile model. While Pharma 3.0 required computerization and connectivity, the transition to Pharma 4.0 asks for data visibility, transparency, predictive capability, and flexibility. This will only be valuable if each of the four elements of the Pharma 4.0 operating model is equally mature.[13]

ii) **Data Integrity by Design:** it has always been a primary focus of regulatory authorities. Since in Pharma 4.0 data travels in multiple directions across the value chain, its integrity faces new challenges. Data transparency is required throughout all product lifecycle. The integration of IT within the company requires well-defined processes and data flows as well as robust, repeatable, and adaptable processes.[13]

Therefore, based on Industry 4.0, Pharma 4.0 is the digitalized operation model within the pharmaceutical industry. In Pharma 4.0, digitization plays a critical role by reducing paper use and establishing a higher level of transparency while assisting faster decision-making. In addition, it enables continuous and real-time control of operations and quality through the use of sophisticated data analytics.[14]

2.2. Artificial Intelligence

Artificial Intelligence (AI) applications have been flourishing over the last few decades, related to the revolution on the field of computer science, since internet was established. However, the term "Artificial Intelligence" was first stated in 1956 by John McCarthy, in a conference he organized at Dartmouth College. Since then it has progressed and the most recent milestone occurred in 2016, when the company Deep Mind, currently owned by Google, released Alpha Go, an AI software that defeated the world champion Go player.[15]

Currently, AI is no longer science fiction. It is embedded in our everyday lives through smartphones, laptops and even watches, assisting humans in a variety of ways. For instance, in saving time in commutes, by analyzing traffic and incidents to suggest the quickest route,

organizing emails, by filtering and classifying them, or giving product suggestions based on recent search and online purchases.[16]

As its name suggests, AI is a computer-processed simulation of human intelligence. It works by processing vast volumes of data while developing rules for analyzing it. Thus, it keeps improving with time by self-correction.[17] This data is then used by AI to uncover patterns and trends that generate insights to enable problem-solving. Additionally, AI has further developed to include the subsets of machine learning (ML) and deep learning (DL) (Figure 4). These operate through AI algorithms that learn from data, allowing them to predict or classify data based on given inputs.[15]

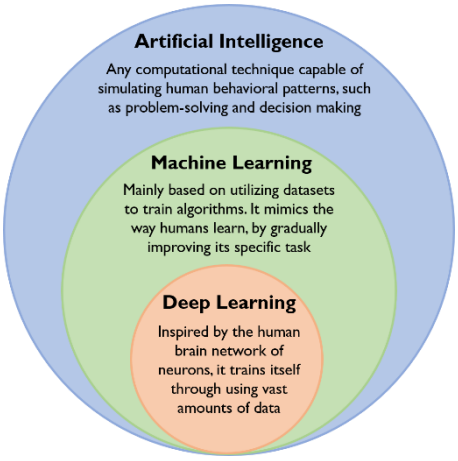

Figure 4: Artificial Intelligence: Deep Learning is a subfield of Machine Learning and both are subfields of Artificial Intelligence.

Machine learning relies on human intervention, often requiring structured data inputs to learn from them.[15] It is classified into three different models:

- **Supervised learning:** Algorithms are taught the desired output through labeled data, in order to classify data or predict accurate outcomes;[18]
- **Unsupervised learning:** Based solely on unlabeled input data, it clusters and interprets it, discovering hidden patterns or data groupings without the need for human intervention;[17,18]
- **Reinforcement learning**: Driven by decision making, it learns through trial and error in a given environment. A sequence of successful outcomes are reinforced to exploit its performance.[17,18]

Deep learning emerged from machine learning, followed by the vast amounts of data it can process and the increasing evolution of computer power. It does not require much human intervention and has the ability to handle larger input volumes of unstructured data. Through data processing, it can generate outputs from numerous layers of nonlinear processing nodes, called neural networks (Figure 5).[15,19]

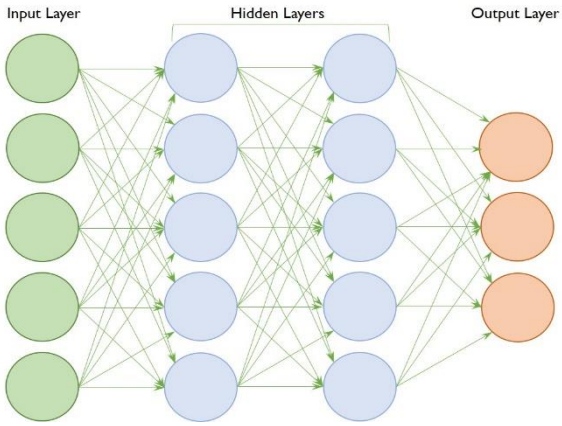

Figure 5: Deep Neural Network (DNN): "Deep" refers to the depth of layers (two or more). Deep learning is a DNN. Simulating the human brain, each artificial neuron sends its output data to another in the following layer, replicating the way human neurons signal to one another.[15]

At the organizational level, AI can improve performance and reduce operational costs by automating operations and business workflows. In R&D, big data and analysis followed by AI models could optimize the whole drug development cycle.[17]

3. Research & Development

3.1. Traditional Model

Pharmaceutical Industry plays a vital role in contributing to the welfare of humanity. In parallel with scientific progress, the healthcare systems continuously demand new drugs in different therapeutic and pharmaceutical areas. As a result, the pharmaceutical industry makes efforts to provide innovative medicines to the market through complex drug discovery and development processes.

Drug discovery final goal is to identify a small synthetic molecule or a large biomolecule with biological activity. It aims to address an unmet medical need by identifying a candidate that could lead to a possible treatment or cure for a particular disease.[20] This process involves several steps, such as: [17,20,21]

1. **Target Identification and Validation**: Comprises the identification of a specific disease, which treatment is not fully addressed. Then, consequently, select a druggable molecular target and proceed to its validation.
2. **Hit Identification**: Hits are compounds that show biological activity against a molecular target. They are usually found through high throughput screening (HTS) of vast chemical libraries, computer simulation, or screening of naturally isolated materials, such as bacteria, fungi, and plants.
3. **Lead Generation and Optimization**: To generate lead compounds, the systematic optimization of hit molecules is initiated. Lead compounds are finally obtained after the demonstrating improved potency and selectivity towards specific biological targets in vitro, as well as improved efficacy and reduced toxicity in animal models of disease. Lead compounds are then further optimized to enhance their effectiveness and pharmacokinetics before moving forwards to clinical development.
4. **Identification of a candidate for further development:** At this stage, the data collected around the molecules allow researchers to choose a target candidate profile that will form the basis of a regulatory submission, finally enabling the candidate to move into clinical trials.

Usually, in an early phase of the discovery process, industry screens about 1 million compounds. In addition, during the following hit-to-lead and lead optimization stages, around 100 compounds are screened to hone one or two candidate molecules, typically from different chemical series.[21]

Once a drug candidate has been shown to fulfill all regulatory requirements during the drug discovery process, as well as promising evidence in terms of mechanism of action, efficacy, and safety, then, the development process for one or few candidates is initiated.

Typically, drug development process includes the following stages:

1. **Preclinical studies**
2. **Clinical trials:**

i) Phase I: Usually performed in a small group of 20 to 100 healthy volunteers, who are closely supervised. The final goal is to evaluate the new molecular entity's (NME) safety, tolerability, pharmacodynamic and pharmacokinetic effects.

ii) Phase 2: Usually performed on a broader population of 100 to 500 volunteer patients living with the target disease. The final goal is to evaluate the therapeutic efficacy and determine the adequate dose level.

iii) Phase 3: The final step in the development process, before regulatory approval. Therefore, these trials are usually performed on thousands of patients across multiple different locations around the globe. The final goal is to demonstrate the therapeutic benefit compared to other existing therapies and confirm the clinical doses and timing of administration.[22]

3. Regulatory phase

The overall process of R&D remains to be a very lengthy, costly, and risky process, with an unquestionably high failure rate in drug development. As a result, on average, in around 10000 molecules synthesized in laboratories, only about one to two molecules are considered to be successful. As it can be observed in Figure 6, the higher levels of attrition are observed at the discovery and preclinical stage, where most of the candidates are eliminated. Still, at the clinical assessment level, the longest and most expensive stage of the development process, the success rates can be considered very low. Thus, adoption of novel models for drug development assumes high priority.

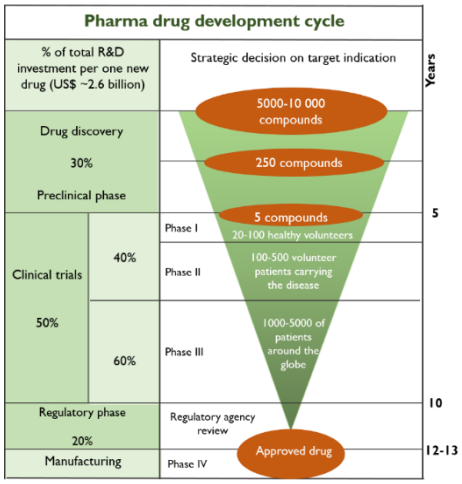

Figure 6: Drug development cycle; Adapted from [49]

3.2. Increased R&D costs and low productivity

Enhancing R&D productivity while reducing expenses is not a recent subject of debate. In 2002, almost 20 years ago, DiMasi referred that new technologies could lead to increased efficiency and innovation, having a significant impact on R&D costs.[23] In the last two decades, from 2000 to 2020, around 671 novel drugs were approved for commercialization by the U.S. Food and Drug Administration (FDA). There was a steep rise in anticancer and biologic drugs approvals which have lately been seen as a major trend.[24,25] Even though the advances in science and drug development are noticeable, the productivity remains low, still including many inefficient processes.

According to the European Federation of Pharmaceutical Industries and Associations (EFPIA) the time-to-market of a new molecule is, on average, of 12-13 years. Ten years are usually allocated to R&D and 2-3 years to regulatory procedures, until the drug is accessible to the population.[5] Due to this long time frame, often researchers who initiate the drug development process are not the ones who end up launching the molecule.

In addition to the long timespan for developing a marketable drug, the average cost, comprising expenses on laboratory research and clinical trials of successful drugs, as well as on molecules that fail to reach the market, was an estimated average of $ 2.6 billion, in 2013.[26]

Furthermore, in the last decades, the pharmaceutical industry has been facing challenges that have directly affected its productivity. The most relevant are:

i) Extremely stringent regulatory requirements;
ii) Increased competitiveness, resulting in a lower return on investment (ROI) due to patent expirations and subsequent market-entry of generics and biosimilars;
iii) Current environmental concerns around industrialization.

These hurdles around R&D in recent years proved that there is an urge for optimization and innovative approaches. Combined efforts regarding new technologies between industry, academic research institutions, and governments will be vital for increasing efficiency in R&D, saving the pharmaceutical industry both money and time, and, most importantly, delivering improved care and quality treatments to society.[27]

In 2020, the surge of the SARS-Cov-2 pandemic emphasized the importance of a digital transition across several different processes and operations in the pharmaceutical industry. Researchers were compelled to move their focus towards the molecular study of the virus. Multiple pharmaceutical companies joined their efforts to develop vaccines in record time, while others focused on repurposing medicines, hoping to find a treatment. Therefore, while the pharmaceutical industry was exposed to a race against time, AI was brought to the foreground as an alternative to accelerate research and regulatory procedures.[28]

3.3. Digital transformation in the drug research and development

In 2020, "ResearchAndMarkets.com" released a report on the global healthcare AI market, estimating it to increase at a CAGR of 41,4%, reaching a market value of about $51,3 billion by 2027. According to the report, this growth is essentially attributed to the increasing financing of AI-based startups in the healthcare sector, supported by the current rising demand for personalized therapies, the positive market effect caused by SARS-Cov-2, the complex

amounts of generated data around healthcare, and the need to reduce costs and improve efficacy.[29]

Therefore, there is no doubt that, in the future, AI will have a huge impact across several stages of the drug development. However, currently such applications are mainly observed at the early stages of drug development process, such as biochemical modeling, bioinformatics or predictive toxicology. Over the last years, pharmaceutical companies have been looking forward to move towards R&D digitalization, though, due to the complex processes, rules and regulations this industry copes with, the overall investment in AI have been insufficient. In addition, most companies are currently overloaded with highly specialized researchers in a variety of scientific fields, yet lacking data science expertise. Since this combination of skills is extremely rare, in order to establish an AI-driven R&D, companies must invest in the development of interdisciplinary teams that complement one another.[30]

However, multiple partnerships between pharmaceutical and AI-driven companies are gaining traction.[17] For instance, in May 2021, Exscientia, an AI-driven pharmatech company, together with the Japanese Sumitomo Dainippon Pharma, announced their second molecule created using AI to enter clinical trials.[31]

3.3.1. Applications of AI in drug discovery

The application of Artificial Intelligence (AI), Machine Learning (ML) and Deep Learning (DL) methods in drug discovery and development can lead to facilitate decision making, accelerate the process and reduce the failure rate.[32]

3.3.1.1. Understanding the pathogenesis and identifying molecular targets

Throughout the years the amount of useful data generated from genomics, transcriptomics, proteomics and metabolomics of both healthy and non-healthy individuals was immense and the tendency for years to come is to exponentially grow. There is a need to capture these data for research and clinical use and make it accessible, so it can be re-assessed. These brings new opportunities to better understand the disease pathway and find new molecular targets. Machine learning can be used to analyze these large data sets in order to establish causality between the target and the disease, and also predict which molecules are more likely to be effective against a specific target while causing less side effects.[32]

A major breakthrough of AI in this early stage of drug discovery, was regarding Amyotrophic Lateral Sclerosis (ALS), a devastating rare neurodegenerative disorder. The dysregulation of RNA-binding proteins (RBPs) is widely accepted as a key factor in the

pathogenesis of ALS. However, there is still no effective treatment for the disease. As a result, IBM Watson, an AI platform from IBM, found five new RBPs linked to ALS disease, within 1467 candidates found in existing literature. IBM Watson did this by text mining all candidates and ranking the most likely to be associated with the disease, based on resemblance to altered RBPs known to cause ALS. The ten most promising candidates were then tested for potential alterations in ALS, using various approaches such as immunohistochemistry, RNA and protein analysis in tissues from ALS patients and healthy tissues, as controls. These validation tests resulted in five RBPs causing significant alterations in ALS tissues compared to controls.[33]

3.3.1.2. Compound Screening and Hit/Lead generation and optimization

The identification of new compounds that interact with molecular targets, as described before, is usually carried out using High-throughput screening, an in vitro technique for testing vast chemical libraries towards a particular target. Yet, due to its expensiveness and low efficiency, emerged the necessity to develop a virtual screening (VS).[34] This *in silico* process has since been widely used to complement HTS in the pharmaceutical industry, biotechnology companies, and academic research.[35] It is mainly used to promote the identification of novel active drug candidates (hits) and turn them into proper drugs by the enhancement of their physicochemical characteristics (lead optimization).[36]

The initial stage in VS is to create a chemical database. Several publicly accessible chemical libraries are widely used as a source, such as ZINC[37] or PubChem[38], each comprising millions of compounds attached to their information. Subsequently, the collected compounds must go through filtering based on different metrics to remove compounds that are unlikely to become feasible drugs.[39]

Afterwards, once the database has been formed, the next stage is to execute the actual screening. This can be attained through two types of VS, a Structure-based VS (SBVS) and a Ligand-based VS (LBVS).

i) **Structure-based Virtual Screening (SBVS):** relies on previous knowledge of the target and ligands structures since it requires the examination of the three dimensional (3D) structure of a molecular target and its ligands.[39] These 3D structures are created through nuclear magnetic resonance spectroscopy of proteins (Protein NMR spectroscopy), X-ray Crystallography (XRC), or computational modeling.[35]

   The purpose of the SBVS is to predict the likelihood of the collected ligands to bind to a drug target. The most widely used technique is molecular docking,

which consists in modeling the interactions occurring between the protein-ligand complex while simulating the binding pose of the ligand in the active binding site of the target. Then, all screened ligands are categorized according to their affinity against the molecular target.[36,39,40] Several software tools can be used to run molecular docking. For example, the open-access AutoDock Vina that gained attention due to its low computational cost and exceptional results accomplished.[36,41] These computational approaches use scoring functions to assess the binding affinity between ligands and molecular targets. However, their success is largely determined by each scoring function they use. Thus, different algorithms tend to obtain distinct results using the same inputs.[42]

Recently, in order to rectify the bias of classical algorithms and scoring functions, several deep learning-based scoring functions (DLSF) emerged to predict binding affinity. Multiple deep learning techniques have been applied, such as a 3D convolutional neural network (3D-CNN) and graph convolutional network (GCN). CNN is used to identify patterns in deep learning, thus 3D-CNN detects patterns regarding binding affinity and pose. GCN is used to assess intramolecular interactions and those occurring between molecules.[42]

ii) **Ligand-based Virtual Screening (LBVS)**: is based on the hypothesis that structurally similar ligands tend to have similar activity towards the same active compound.[42,40] Therefore, contrary to SBVS, it does not require previous knowledge of the structures.[39] Instead, it relies on prior knowledge of molecular and chemical features of the ligands. By comparing the structural similarity between potential ligands and known active compounds, the LBVS method is able to discover novel ligands.[40]

One of the mainly utilized approaches in LBVS is the quantitative structure-activity relationship (QSAR). It evaluates the correlation between ligand physiochemical attributes and its bioactivity. This model provides an early *in silico* assessment of key characteristics such as activity, toxicity, and selectivity of potential drugs. This *in silico* evaluation plays a significant role in lead optimization by considerably reducing the number of candidates tested *in vivo*.[40]

A recent practical example for hit identification was performed by an AI-driven drug research startup called Atomwise. They developed AtomNet, the first structure-based deep convolutional neural network. This model learned to predict binding affinity using millions of small compound bioactivity values and thousands of protein structures. Since it is based on

deep learning, it does not require much previous knowledge neither about the target or the ligands. When researching for potential inhibitors for a Canavan Disease promising target, this approach started from a chemical library comprising 10 million commercially available compounds and successfully screened them down to five potential low-micromolar inhibitors.[43]

3.3.1.3. *De novo* drug design

The early use of machine learning models in drug design was initiated with VS methods. However, through the development of data science and the enhanced accessibility of public data in recent years, ML brought a new paradigm to de novo drug design.[44]

The aim of de novo drug design is to create new drug-like compounds with specific properties.[45] Nowadays, it has evolved to the use of state-of-the-art DL-models, such as the example of Generative Adversarial Networks (GANs). GANs models came out as a groundbreaking approach, which have been broadly applied in artificial image generation. This model is composed of two interconnected neural networks - a generator and a discriminator, that learn from each other, improving their skills over time (Figure 7). Hence, the model ends up designing structures that can lead to novel molecular compounds.[44,46]

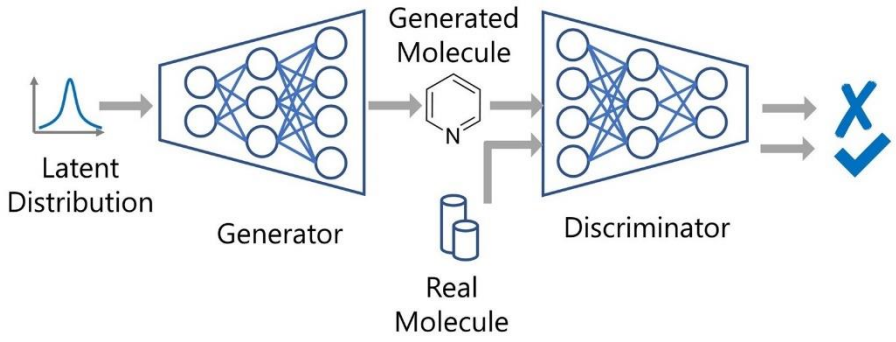

Figure 7: Generative Adversarial Networks: It contains two neural networks that are trained simultaneously, by competing against each other. There is a generator (G) and a discriminator (D). While G generates different chemical structures, D is provided with both generated data from G and real data. Thus, D works as a binary classifier, learning to accurately distinguish the generated examples. Simultaneously, D gives feedback to G that will improve its capacity to generate more realistic structures and consequently increase the difficulty for D to distinguish if they are real or false. This way, both networks are trained and improve their capacities over time. Eventually, even though D identifies the slightest variations between real and generated molecules, G will create structures that D cannot recognize the difference. [44]; From [127]

Insilico Medicine, an AI biotechnology company based in Hong Kong, announced in 2019 the development of GENTRL, a Generative Tensorial Reinforcement Learning platform that combines two distinct modern AI techniques: GAN, already described above, and

Reinforcement Learning (RL), a machine learning training technique capable of interpreting its environment, taking actions, and learning by rewarding desired actions and penalizing undesired ones.[47]

Initially, GENTRL was used to find inhibitors of discoidin domain receptor 1 (DDR1), a pro-inflammatory receptor involved in fibrosis. It was programmed to rapidly design novel compounds with activity against DDR1 kinase from a vast database containing molecules from a ZINC data set, known DDR1 inhibitors, common kinase inhibitors, and others. Then, 3 RL algorithms were used that acted as filters and obtained an initial output of 30.000 structures. These were then narrowed down to 40 structures for analysis, and afterwards 6 different lead candidates were found to have the highest inhibition activity against human DDR1 kinase. What would have taken 2 to 3 years following the traditional approach occurred within 46 days using AI. Throughout this period, the saved time could thus be used to design, synthesize and experimentally validate the leads in vitro and in vivo, proving the potential of AI in the drug discovery process.[47]

3.3.2. Applications of AI in drug development

The adoption of AI in the drug development cycle has progressed more rapidly in drug discovery than in clinical development. The reason is mainly due to the use of *in vivo* cell assays and animal models in drug discovery, which vastly reduce the regulatory concerns when compared to testing potential drugs in people.[48]

3.3.2.1. Clinical development

The overall efficiency and effectiveness of the existing clinical development model still has much space to improve. During the drug development cycle, clinical development is the most time and money-consuming phase. Almost half of the total time and cost in R&D is spent during clinical trials. Moreover, the high failure rates are one of the main obstacles for innovation, frequently leading companies to find it too risky to invest and end up giving up or choosing a safer path.[49]

AI holds the potential to improve a large set of processes within clinical trials. Thus, large biopharma companies are now joining efforts to identify current issues and find solutions to transform the traditional approach. Most of them are starting to invest in AI methods and other digital technologies, by acquisitions and partnerships, to accelerate drug development and innovation, by reducing burden in different steps of the process.[48]

Therefore, in order to improve the success rate of drug development, there have been identified two different approaches where AI can have an impact, that will be further discussed in the following sub-sections.

3.3.2.1.1. Scientific approach

The first one is the scientific approach, whose primary purpose is to find better monitoring biomarkers for clinical research. These biomarkers can be used to develop more precise and efficient medicines through evaluating and measuring the response of the patient to the experimental treatment during the clinical trial.[50]

As an example, clinical trials around Parkinson's disease (PD) are beginning to move towards a more personalized approach through the use of ML models. PD is a chronic neurodegenerative disease affecting 2-3% of the population above 65 years, that comprises a wide range of symptoms including both motor and non-motor disabilities.[51,52] Usually, in clinical trials, the way to diagnose and monitor PD patient symptoms use very obsolete and subjective methods.[51] They are assessed in the clinic by a physician, primarily using the 1980's Unified Parkinson's Disease Rating Scale, revised in 2008 by Movement Disorder Society (MDS-UPDRS). This scale was assembled to contribute to both patients and physicians in order to measure several non-motor and motor experiences of daily living, thus assessing disease progression over time.[53]

However, this scale has gradually been found to hold a few characteristics that affect its reliability. Firstly, it can be very subjective since different physicians can come up with different results based on their own perception of the disease. Secondly, since the patient's visits to the clinic occur between significant time span periods, it becomes challenging to continuously monitor the progression of the disease because, in the meantime, the patient usually ends up missing a lot of relevant information. Moreover, the information provided is not accurate because there is no molecular biomarker to be used. [51]

To address these issues, in recent years digital technology came up with a new class of biomarkers, described as "digital biomarker". Clinical development can now go further outside the clinical setting in remote-controlled studies through sensors and computational tools from mobile devices, such as smartphones, smartwatches, or wristbands. Thus, it can study the daily progression of PD and symptom severity in real-world settings.[50,54] This neurodegenerative disorder is particularly suited to the use of digital biomarkers due to its vast motor symptomatology (*e.g.,* tremors, muscle rigidity, bradykinesia, posture and gait issues, impaired coordination, speech and swallowing difficulties) alongside with side-effects to current dopamine treatments, such has dyskinesia.[55,52] Patients can be monitored through these

biomarkers, thanks to the use of motion sensors like accelerometers and gyroscopes, that allow researchers to directly understand patient's daily routines, symptoms burden, and drug response.[55]

However, these biomarkers still require laborious verification and validation processes due to the complex interplay between engineering, data science, health information technology, and clinical research. [50] Currently, Big Data integrated with DL-methods is frequently used to allow computational models to learn from the collected data, identify patterns, and make decisions without human intervention[56]

In order to comprehend the impact of Big Data in drug research, most specifically on clinical trials, emerges the need to better understand its concept. Big Data is mainly characterized by four Vs. The first and more evident one is the volume, due to the vast amounts of data comprised within a data set. Which then leads to its variety, since the data can be both structured and unstructured, depending on its origin. Velocity is also of great importance, regarding the speed needed to analyze large portions of data, ultimately leading to decision-making. Finally, the fourth characteristic is the veracity, due to the fact that, when processing data, it must provide trustworthy outcomes.[57]

The recent noteworthy advances in computer science, namely in data storage, processing capacity, and most importantly the development of machine-learning and data mining approaches, propelled Big Data even further. It improved its use, by enabling vast amounts of data to be analyzed and used to identify patterns more accurately. In the pharmaceutical sector this brought new opportunities, for instance in identifying patterns related to drug therapy or disease risk.[57]

In clinical trials, different types of data can be generated, such as raw, structured, and unstructured data. These data sets can be related to the individual biology, its genetics, clinical assessments, or even data correlated to the patient environment and lifestyle. Big Data platforms gather this information from various sources and use analytical methods to develop models that can be then used in diverse applications regarding clinical development.[57]

Hence, Big Data analyzes can transform Real World Data (RWD) into Real World Evidence (RWE). As described earlier, RWD stands, for example, as the data collected from wearables, the digital biomarkers in Parkinson's disease trials. RWE is what results from the analysis of RWD and ends up being used to generate knowledge and assist health care providers in decision-making, allowing them to assess the benefit-risk of the experimental drug.[58]

3.3.2.1.2. Operational approach

Then, in addition to the scientific approach, there is the operational approach. When it comes to the operational processes, recruitment, and retention of eligible patients to enroll in clinical trials remain the major challenge:

- 86% of trials fail to comply with enrolment agenda;[59]
- 32% of all Phase III trials end up failing due to enrolment issues;[59]
- Patient recruitment is the most lengthy process, taking up to one-third of clinical development extent.[60]

The remote-controlled studies using digital biomarkers can also have a considerable impact on patient recruitment and retention due to the low travel burden for patients, which can otherwise be remotely monitored without often traveling to the clinic. Particularly, when persuading elderly patients to participate in trials, frequent travels are perceived as a huge drawback.[61]

Big Data can also play an important role in enhancing these processes. It could contribute to gathering vast amounts of information to assist in the identification of individuals with a particular disease, based on their "digital footprint", including electronic health records (EHR), prescription data, clinical trial data, laboratory data, and genetic features, taking into account patient privacy. Furthermore, it would improve comprehension and validation of medical expectations regarding the population of interest. such as information about disease characteristics or operational characteristics like clinical trial design, clinical endpoints, retention and response rates, and study extent.[62]

Another hurdle for patient recruitment, retention, and compliance is that patients are allocated the placebo, particularly in cases when the trial is the only chance for them to receive treatment. A solution for this challenge, may be to design single-arm trials, assigning all patients to the experimental drug. When opting for a single-arm trial, researchers are lacking a control, that ends up limiting their comparative data. However, to counter this issue, they are developing historical controls, based on data from published literature. In addition, in order to improve evidence, there is increasing interest on searching for an external comparator using RWD. The fact that all patients would receive the active treatment would certainly improve recruitment and retention rates.[62]

Retention rates can also be increased by close monitoring of patients and continuously giving them assistance, making sure that they remain compliant. As an example, AICure, a U.S. based company focused on the development of digital solutions to improve clinical trials, developed a mobile software that was used in a Phase II trial in patients with schizophrenia,

which works by monitoring patient regular drug intake, ensuring that the protocol was being followed. It was a success, revealing a 25% increase in adherence.[17]

As highlighted above, the use of Big Data and AI models will be critical to improve clinical development. However, these approaches still pose some limitations. Although companies are now joining strengths to adopt IT solutions, this requires a high level of expertise and internal investment that pharmaceutical companies will have to rapidly cope with, since there is still no adequate IT environment. In addition, when it comes to processing data, despite recent regulatory efforts to empower patients to have more control over personal data, there are still some concerns regarding data security and patient privacy.[63]

3.3.2.2. Drug repurposing

Drug repurposing has been a widely used strategy to optimize drug development. It is focused on reusing approved or even clinically failed drugs for the treatment of a new therapeutic indication. Thus, instead of going through all the lengthy and expensive stages of drug discovery, it goes directly to preclinical testing and clinical trials neglecting the initial steps of drug discovery and safety testing that a new molecular entity has to go through, making the development more efficient while spending less.[64]

Recently, regarding the SARS-Cov-2 pandemic, drug repurposing emerged as a powerful solution to fasten the identification of possible drugs to treat the disease. In the midst of a worldwide crisis, the de-novo drug discovery lengthy process was inconceivable to find a treatment in such a short period of time. Thus, the pandemic came as a great opportunity to develop AI methods in this specific domain of drug repurposing. However, there are several challenges to surpass when repositioning a drug. The reasoning behind drug repurposing is that a preconceived drug for a specific disease might have the ability to target another disease, due to shared interactions. Since drug targets do not function isolated from the complex cellular mechanism, it is pivotal to understand beforehand the interactions that may occur between each drug-target complex. For instance, SARS-CoV-2 needs several different host cellular proteins to succeed during infection.[65]

Therefore, several studies regarding drugs that target these host proteins were conducted to repurpose old drugs for the treatment of SARS-CoV-2. That was the case led by BenevolentAI. The company developed a knowledge graph, which is a repository that integrates biomedical data from structured and unstructured sources as well as scientific literature extracted by ML. By searching for approved drugs that could potentially block viral infection progression, they identified baricitinib, a drug used in the treatment of rheumatoid

arthritis. Baricitinib inhibits proinflammatory factor Janus kinase 1 and 2 (JAK1/2), but has also shown high affinity to the AP2-associated protein kinase 1 (AAK1). AAK1 is known to be one of the regulators of endocytosis. Thus, by inhibiting both proteins, baricitinib could interrupt the entry of the virus into the cells and also fight the cytokine storm, known as the prominent cause of death in patients with SARS-CoV-2.[66,67]

Regarding these positive outcomes from the AI-driven approach, baricitinib was suggested to enter clinical trials. The most relevant trials were conducted in combination with remdesivir, an antiviral drug that was shown to be effective for hospitalized SARS-CoV-2 patients. Compared to remdesivir monotherapy, the results revealed improved outcomes. The recovery time was reduced from 18 to 10 days among patients receiving high-flow oxygen or noninvasive ventilation while also decreasing the number of serious adverse events. In July 2020, the trials were completed [67,68]

At the beginning of the pandemic lives were being lost due to a lack of treatment options. Today, several repurposed drugs proved to be effective against the virus, such as remdesivir, dexamethasone, baricitinib, and others, and were approved to the "COVID-19 Treatment Guidelines" of the U.S. National Institute of Health.[69]

4. Supply chain

The pharmaceutical supply chain comprises a complex network of resources, transactions and processes that connect different players, such as suppliers, manufacturers, distributors, retailers, as well as information and logistic services providers. Starting from the raw materials, the final goal is to provide the finished product to the consumer.[70]

4.1. Pharmaceutical supply chain and the effects of globalization

Throughout the last two decades, we have been witnessing the growth of globalization followed by huge technological advances. In 2000, the total value of goods exported across the world stood around 6.5 trillion U.S. dollars, while in 2019 it almost tripled to around 19 trillion dollars (Figure 8).[71]

Figure 8: Worldwide export value of goods from 1960 to 2020. Adapted from [71]

These increase throughout the years triggered the current competitiveness and highly demanding global market. Where velocity, quality and quick responsiveness play key roles in consumer satisfaction. As consumers have more access to information than ever before, companies need more agility to fulfill their unique and unpredictable needs.[72]

Furthermore, the pharmaceutical market has an exclusive supply and demand nature with both clinical and economic interests from patients, governments and companies. Consequently, the pharmaceutical sector must ensure that its supply chain is running without further delays, in order to avoid shortages and meet patient demand.[72] Hence, digitalizing and automating supply chain operations will certainly contribute to saving resources by the pharmaceutical industry, which could then be allocated to more meaningful areas. [73]

In the beginning of 2020, SARS-CoV-2 pandemic brought to the foreground many issues and questions regarding globalization and consequently the global trading and supply chains. The first country to lockdown was China, which is a major player in the global supply chain, sustaining around 17,4% of global Gross Domestic Product.[74] Its rise over the previous decades has been fueled by China's huge market, which now comprises more than 1,4 billion people[75], as well as continuous investment in industrial capacity and an aggressive competitiveness based on cheap labor costs.[76] As a result, China became one of the major producer of drug ingredients, having a strategically vital role in the pharmaceutical sector. The impact of China's lockdown and the consequent movement restrictions across borders due to the pandemic greatly affected the global supply chain, leading to supply shortages. In February 2020, 94% of the Fortune 1000 companies reported to have felt supply chain disruptions related to SARS-CoV-2 outbreak.[77] Even though this crisis imposed significant

constraints in the pharmaceutical sector, companies rapidly focused on identifying associated risks and threats and started searching for alternatives. What was once a challenge became a chance for change.[78]

After assuring operational and resources sustainability, as well as labor safety and availability, the goal was established to transform operations, including the supply chain, into digitally enabled systems.[79] Although this shift towards the Industry 4.0 gained higher relevance in the pandemic environment, as described in section 2., this concept was first introduced in Germany in 2011 and has since began to be adopted by several pharmaceutical companies.[80]

4.2. Supply chain digitalization

Due to the increased competitiveness, the industry has recognized that improving supply chain management (SCM) could reduce costs by optimizing resources and processes associated with logistics, production, and inventory, thus increasing profitability. Additionally, it would provide competitive advantages by allowing companies to further invest in innovation, product launch, and customer value.[81]

In present era, cutting-edge technologies like blockchain and artificial intelligence (AI) could provide supply chain a superior end-to-end visibility, robustness, and adaptability.[79] Industry 4.0 is predicted to transform supply chains to smarter systems that can trace individual products, improve security and transparency, as well as maximize economic gains and reduce environmental impacts.[7] However, it has not been yet adopted by most supply chain players and there are still many challenges to overcome within the pharmaceutical supply chain. In order to surpass these obstacles, the blockchain is a disruptive technology capable of providing high-end traceability, robustness and resilience to the supply chains. [79]

Therefore, in the following sections, challenges and potential solutions regarding counterfeiting prevention (namely through serialization), blockchain technology and e-commerce, will be discussed.

4.2.1. Counterfeit and Serialization

In 2011, the European Parliament recognized an alarming issue regarding the increase of falsified medicinal products being marketed both through legal and illegal markets. Those products were identified as containing substandard or fraudulent ingredients, incorrect dosages, or even no ingredients at all, presenting severe risks to public health.[82] Thus, the European Union's Falsified Medicines Directive (FMD) 2011/62/EU was developed, envisioning

to protect patients by preventing counterfeit medicinal products from entering the pharmaceutical supply chain.[83,84]

A series of studies conducted by the Organization for Economic Co-operation and Development (OECD) and the European Union Intellectual Property Office (EUIPO) found that, out of 97 product categories, pharmaceuticals were the 10th most counterfeited ones, reaching a global trade of estimated $4.4 billion in 2016.[85] Also, even though the global issue was officially recognized 10 years ago, the numbers are still increasing. From 2014 to 2018, the number of annual incidents reported related to counterfeit drugs increased by 102%.[85] According to WHO, the most affected are the developing countries, with average market shares of counterfeit and substandard medicines estimated at around10.5% (Figure 9). However, since most of these drugs are sold in illegal markets, reliable data on the health and socioeconomic impact is sparse, probably underrepresenting the full extent of the problem.[86]

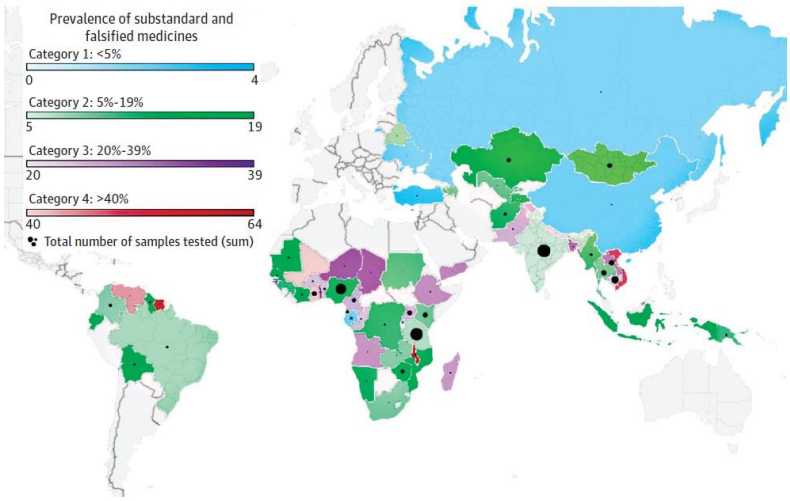

Figure 9: Prevalence of Substandard and Falsified Medicines in the World; From [87]

Although there are many reasons for the development of these counterfeit markets, like the access to prescription drugs and the drug cost, two stand out [84]:

i. The inefficiency of the regulatory mechanisms, which for example, by allowing parallel trading, contributes to the appearance of counterfeit medicines. Thus, also leading to the increased complexity of the supply chains and routes of transport, making it very difficult for national authorities to trace back the products' history or source;
ii. The increasingly globalized markets and supply chains powered by e-commerce, that serve as a gateway for illegal trading of pharmaceutical products.

The solution to the identified problem stated in the 2011/62/EU Directive was then detailed in the Commission Delegated Regulation (EU) 2016/161. This regulation established

"detailed rules for the safety features appearing on the packaging of medicinal products".[87] The main requirement is designated "serialization". It involves the assignment of a Data Matrix Code associated with a unique serial number, a Global Trade Identification Number (GTIN), an expiration date, and a batch number, in each individual package (Figure 10).[83] Thus, reading the code with an IoT device gives access to the identification and authentication of the products guaranteeing its end-to-end verification.[84]

Figure 10: Representation of the serialization of a package; From [88]

The regulation concerning "serialization" came into force on 9th February 2019. It has impacted the entire pharmaceutical supply chain, from active substance manufacturers to pharmacists dispensing medicines.[87] However, it was noticed that prior to each shipment, the pharmaceutical manufacturer must report all serial numbers of the products introduced into the supply chain to a central regulatory body, such as the European Medicines Verification Organization in Europe (EMVO). In addition, as safety and reliability regarding the quality of the product and the related transactions are guaranteed by the central authority, all players are called to retain a relevant amount of data about the products for several years, particularly the one related to their own responsibility. Thus, all the players have the responsibility for communicating with the regulatory body, that plays the role of authority.[83] Although the ultimate goal is to increase trust through a greater transparency and improved capacity to detect fraudulent activities, serialization remains insufficient to eliminate fraud, as there is still a possibility of data manipulation.

For that reason, blockchain appeared as a promising technology in the supply chain. Its underlying distributed ledger technology makes it capable to prevent fraud, while providing high-end traceability, robustness and resilience to the supply chains. [89]

4.2.2. Blockchain technology

Satoshi Nakamoto invented the first blockchain network in 2008 when the author/s released a white paper about the concept of Bitcoin, which used blockchain technology to

create the first cryptocurrency, a peer-to-peer[1] electronic cash system.[90] More recently, fueled by the increasing cryptocurrency market capitalization, it has sparked a surge of excitement, being heralded as the new technological revolution after the Internet. [91]

There is no standard definition for blockchain. However, as its name suggests, it consists of a chain of blocks.[92] These blocks store and share data from multiple peer-to-peer transactions, in a decentralized, transparent, and secure way. [92,93,94,95]

As a result, rather than storing all data in a centralized database, such as the traditional cloud-base applications, the data is stored and validated in a distributed and synchronized network across all participants (Figure 11).[96,97]

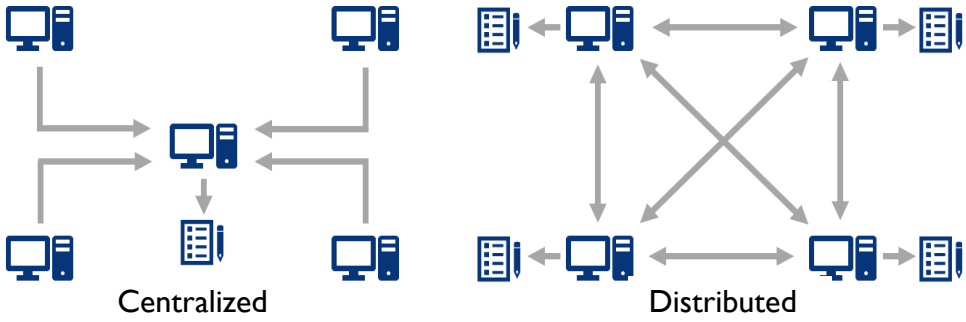

Figure 11: Representation of Centralized and Distributed Networks: Data is stored and exchanged with all allowed users, providing each one with a replica of the information. Every time information is added in the network, the replica is instantaneously updates. Thus, it eliminates the need for an intermediary to transfer information to each entity. Data is secured by using cryptography, a mathematical technique for hiding and disclosing information, which guarantees that only the designated recipient can have access to the content.[97]; From [97]

Other important characteristic of the blockchain technology relates to its immutability. This means that all data stored in the blockchain is tamper-proof. To guarantee data immutability, three technologies are combined: digital signatures[2], hashing, and a consensus mechanism[3].[98]

Therefore, when a participant wants to make a transaction, the transaction is added to a new block alongside all transactions at that time. Since it is a distributed network, the transaction is transmitted to all network nodes or miners, that compete between each other

[1] Peer-to-peer is the concept behind online transactions that are sent directly from one party to another without going through an intermediary institution.[90]

[2] Each network participant holds a pair of keys: private and public key, which when combined create a digital signature. If a participant wants to make a transaction, the transaction needs to be signed with the private key. The public key is then used by other participants, when verifying the transaction.[97]

[3] A consensus mechanism (e.g. proof of work or proof of stake) is a method that occurs through a theoretical computer science problem. It ensures all nodes are synchronized and agree on predefined conditions and rules. If all the participants agree on the transaction, the block is added to the chain. [124,125]

to solve a complex mathematical problem, using cryptography algorithm. When the problem is solved, the solution is transmitted to all participants, that need to agree, through a consensus mechanism, on the legitimacy of the transactions included in the block. Then, the new block is added to the chain.[95,93] Hence, once a transaction is validated, it cannot be modified without breaking cryptographic links across the whole network.[92,93] This occurs due to a process called hashing. Besides the transactions data, each block also includes its own cryptographic hash value[4] and the hash value of the prior block, creating an unbreakable dependency between. Since hash values are unique, fraud can be successfully avoided because a transaction in a previous block can only be updated by adding a new block to the chain. Unlike centralized systems, the blockchain network continues to operate even if individual nodes fail.[95] A simple representation of how a transaction is processed in the blockchain, is shown in figure 12.

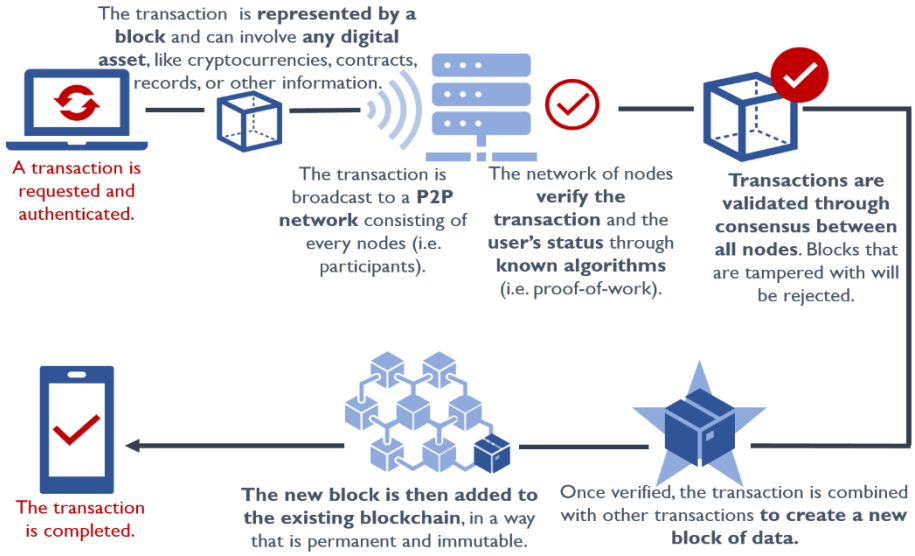

Figure 12: How Blockchain Works; Adapted from [128]

Blockchain technology promotes trust between participants since they only need to build confidence in the system, bypassing the trustworthiness of other network participants. The nonexistence of intermediaries also enhances data security since it decreases the risk of private data leaks to the public. Thus, with blockchain, supply chain intermediaries may become obsolete, ultimately improving user security. [95]

[4] A hash value is an encrypted, non-readable string of numbers and letters, that represents the data from the transactions contained in each block. It can be used to identify and confirm the execution of a transaction. Once a block is created its hash is calculated, thus changing data inside the block will cause the hash to change – useful to detect changes in the block. [96]

4.2.2.1. Blockchain Applications in the supply chain

While blockchain technology has been unveiling its potential in a variety of sectors, its widespread use beyond the well acknowledged use in cryptocurrencies is still in its infancy.[94,99] For pharmaceutical industry supply chain, most use cases are still being researched and running pilot projects.[94] The expectations for its utility in the healthcare sector are high, including the improvement of security, privacy and interoperability as well as its potential to place patients in the center of the ecosystem.[99]

4.2.2.1.1. Traceability and Transparency Enhancement

Traceability and transparency throughout the supply chain are critical components to have safe medicines and the basis to foster patient trust in the pharmaceutical industry.[83] However, in today's worldwide supply chain systems, it is challenging to have visibility towards all transactions occurring from the origin to the end-consumer.[100] Data about financial or product transactions is usually stored in multiple locations, only accessible to certain entities.

As a result, the most widespread blockchain implementation in supply chains is to enhance traceability and transparency throughout the whole process products undergo. It starts from verifying the origin of products, including their location, date of transaction, and responsible person or entity, lasting through the process of recording data about their route and each transaction that occurs.[94]

As discussed in section 4.2.1., a major problem running through the pharmaceutical supply chain is the presence of substandard, ineffective, or falsified medicines manufactured with the intent of misleading the public about their legitimacy and origin.[99,101] This issue is more prevalent in low- and middle-income nations owing to inadequate pharmaceutical governance, weak technical competence, and reduced supply chain management.[102]

However, the problem is not exclusive to these countries. As an example, on February 2012, the FDA detected counterfeit versions of the biological anticancer drug bevacizumab (Avastin®, Genentech, U.S.) introduced in the U.S. supply chain. This drug is used to inhibit tumor growth and was the ninth highest-grossing medicine in the world in 2013, having generated around USD $ 6 billion in sales. The counterfeit versions detected had no active pharmaceutical ingredient (API), instead containing substances such as corn starch, salt and typical solvents, like acetone. As expected, this incident represented a turning point in the U.S. and international drug safety history, exposing global supply chain vulnerabilities to falsified drug dissemination.[101]

Following this event, similarly to the European Union's Falsified Medicines (FMD) Directive, in 2013 the U.S. came up with the Drug Supply Chain Security Act (DSCSA), that plans to build an electronic, interoperable system to track and trace prescription medicines in the United States until 2023, in order to protect patients against falsified, stolen, contaminated, and dangerous drugs.[10388] The intention of the law was set to allow pharmaceutical partners cooperating on the enhancement of patient safety. Thus, in 2019, FDA released the DSCSA Pilot Project Program, which was designed to support the stakeholders in the creation of an electronic, interoperable system for identifying and tracking prescription medicines through the distribution chain.[103]

As previously reported, the first implemented process towards traceability was the serialization of medicines. Currently, pharmaceutical manufacturers are required to store the encoded data in a corresponding electronic record, to be used for verification requests. Though in the near future, this data must be shared between distributors, third-party logistics providers (3PLs), packagers, and dispensers, as the product travels through the supply chain.[88] In order to guarantee authenticity, a safe link between the actual product and its digital identity must be settled. Thus, the link could be established using serialization for identity authentication and a blockchain-based solution to store the digital identity.[97]

Therefore, in March 2019, four companies (Merck, Walmart, KPMG, IBM) with different roles across the pharmaceutical sector gathered round as a response to the FDA's Pilot Project Program. Thus, during six months, the consortium conducted the Blockchain Interoperability Pilot Project. The main goals were to test the effectiveness of blockchain in the verification and tracking of pharmaceutical products and resultant detection and report of suspicious ones, while adapting for future DSCSA interoperability requirements. The companies considered that with shareable records, data immutability, and ability to trace medicines, blockchain technology was exceptionally capable to solve several problems associated to the pharmaceutical supply chain. [88]

The Pilot Project was tested across participants with distinct roles in the supply chain, namely a manufacturer, a distributor and a dispenser. Thus, it demonstrated that blockchain technology enabled a decentralized, trustworthy method of sharing information between different network stakeholders, thus paving the way for compliance with the DSCSA 2023 interoperability standards. The solution shown to be promising in tracing individual packages across the supply chain, while preventing fraudulent practices through the verification of authenticity and prompt identification of suspicious medicines (Figure 13).

In addition, it also proved ability to integrate the Pilot solution with the running operating systems of the different participants, without imposing significant burden, which is critical for achieving high levels of interoperability.[88] Nevertheless, such digital transformation requires constant research and flexibility as technologies are developed.

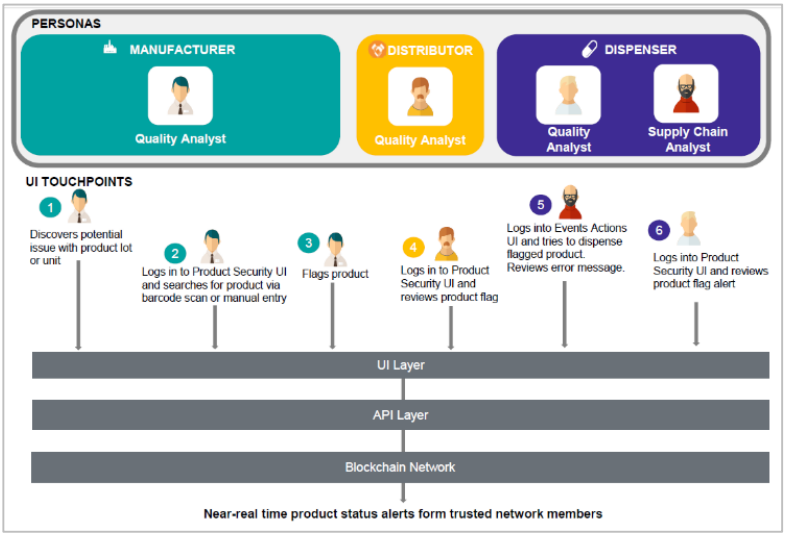

Figure 13: Blockchain Interoperability Pilot Project: Representation of how operators can verify product authenticity and flag suspicious medicines preventing them from being shipped or dispensed; From [88]

The business value of a digital record tracking the flow of products across the supply chain unlocks the possibility for addressing other critical issues. An example could be to improve the cold chain logistics with IoT sensors and smart contracts, as discussed in the next section.

4.2.2.1.2. Transaction automation and the optimization of the cold chain

Trust is a vital component in the supply chain, being traditionally developed over time as companies collaborate effectively, exchanging different kinds of information. In today's complex industrial ecosystem, players often lack familiarity with one another, resulting in poor visibility and trust, which then must be developed elsewhere.[104]

For that reason, smart contracts have proved to be a method for establishing a trustworthy system. Having emerged from Ethereum, an open software platform based on blockchain technology, it allows developers to create decentralized software applications on the blockchain layer.[105] *Smart Contracts* are digital agreements between parties that automate specified actions when predetermined contract conditions are satisfied, therefore ensuring the performance of frequently unfamiliar suppliers. As a result, traditional methods of building confidence are bypassed.[83,104,106]

Since *Smart Contracts* are stored on a blockchain, they inherit its immutability, and distributed nature. That means the contract's output is verified by everyone on the network, eliminating the need for a certified entity, like a bank, broker or lawyer, to serve as an intermediary. Therefore, the transaction itself becomes more efficient and less expensive, diminishing chances of mistake and disruption during execution.[94] Due to its simplicity and speed, companies could reduce costs and save time, which is particularly critical when it comes to supply chain and logistics.

This method could be used for a broad variety of transactions, for instance the delivery from raw materials to the finished product, for the payment of value-added services, the transfer of the Intellectual Property (IP) value, or for paying insurance.[94,104] Although the technology is mostly in a testing phase, *Smart Contracts* are expected to have success in logistics and supply chain management in the near future.

A critical issue the pharmaceutical sector is currently dealing with is the struggle to manage the cold chain, which, according to IATA (International Air Transport Association), is responsible for approximately USD $35 billion in losses due to temperature excursions.[107] Additionally, the recent trend toward biologic and biosimilar medicines, as well as precision medicine, means that the majority of novel and high-value drugs will tend to be more sensitive, requiring improved cold chain handling and specialized, temperature-controlled logistics.[78] As a result, the "Pharmaceutical Commerce" projection indicates that the sales volume for these highly sensitive medicines are increasing at over twice the rate of the overall industry, with projected worldwide sales of $416 billion in 2022, accounting for 29% of total sales volume (Figure 14).[108]

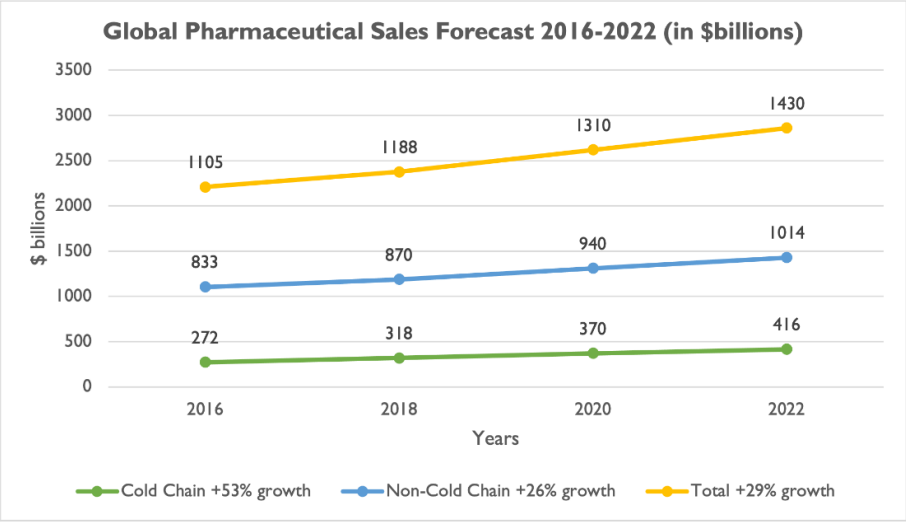

Figure 14: Global pharmaceutical sales forecast from 2016 to 2022; Adapted from [108]

Correspondingly, the rules regulating the distribution of medicinal products for human use are becoming more stringent. The EU guidelines concerning the "Good Distribution Practice (GDP) of medicinal products for human use", *(GDP 2013/C 343/01)*, require companies to have a tight control on potential risks or deviations concerning environmental factors. According to the guidelines, the supplier has the responsibility to "ensure that temperature conditions are maintained within acceptable limits during transport". Also, in order to comply with the requirements of GDP, "it should be possible to demonstrate that the medicines have not been exposed to conditions that may compromise their quality and integrity".[109]

The quickest solution found to fulfill the criteria was through costly, temperature-stabilized trucks and containers from third-party logistics providers (3PLs), which proved to be excessive for the majority of medicines, which are not sensitive to minor temperature variations.[110] That resulted in the creation of Modum, a startup based in Zurich, that developed MODsense, a system incorporating a temperature monitoring and tracking solution for the transportation of pharmaceuticals. It combines IoT sensor devices, that can monitor and record temperature throughout the transit process, providing real-time data, with blockchain technology, which enables the execution of *Smart Contracts*.[111] Thus guaranteeing that the temperature records stay immutable and that *Smart Contracts* are created for each shipment, providing a reliable method to ensure compliance with the regulatory requirements.[73,83]

As an example, if a disruption in the supply chain occurs, such as in the case of a pandemic situation, the industry requires improved visibility and adaptability. If a container is transporting highly sensitive medicines, requiring certain temperatures, a delay in delivery may damage their quality. However, by using IoT real-time monitoring sensors attached to the products, stakeholders are able to monitor product stability. If the regulatory requirements, such as on-board temperature, are not fulfilled, then the predetermined rules in the *Smart Contracts* are also violated, causing an alarm to be triggered. Then, almost instantaneously, the stakeholders involved in the transaction are warned that there is an anomaly, allowing them to accelerate their decision-making process.[110,111] Figure 15 illustrates the end-to-end shipping process using the MODSense system.

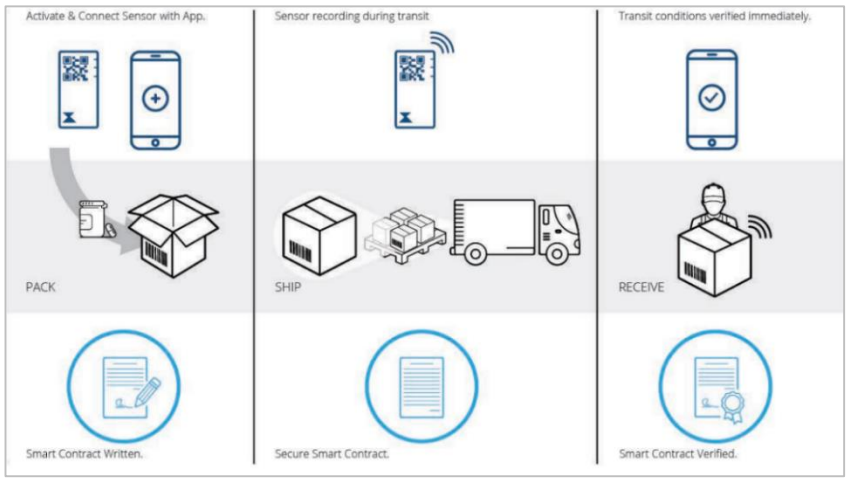

Figure15: MODSense (Modum IoT-blockchain system) shipping process; From [110]

4.2.3. Commercialization to the end-consumer: moving towards e-commerce

4.2.3.1. Amazon aiming to disrupt retail pharmacy business

In 2017, Amazon was approved to distribute medicines in at least 12 U.S. states, causing a certain commotion around major pharmaceutical supply chain players. While that didn't necessarily mean Amazon would begin selling prescription medicines, the approval was enough to strongly impact the retail pharmacy stock market.[112]

Subsequently, Amazon masterplan to enter the pharmaceutical market was boosted in 2018 with the acquisition of Pillpack, a "online pharmacy" startup, for approximately $753 million.[113] Thus, strongly representing the company's commitment to break into the healthcare sector.

Finally, in November 2020, Amazon extended its remote pharmaceutical service further when it introduced Amazon Pharmacy in the United States. PillPack's infrastructure was used in part to build the service. Nonetheless, PillPack continued to operate as a separate service within Amazon Pharmacy. This is because PillPack was designed for a distinct purpose, providing medications to patients with chronic disease who often take several medications daily.[114,115] Amazon Pharmacy, however, is taking on the standard pharmacy service, providing generic and brand medicines in bottles, expanding into new segments of the industry, such as serving patients with acute medication needs or even by adding physical pharmacies to its retail stores, such as Whole Foods Market.[116]

PillPack is currently licensed in 49 states around the U.S., which allows it to ship and operate its mail-order business. Their main focus is to provide a convenient service, by delivering a customized multi-dose drug dispensing (MDD) package directly from the warehouse to patient homes. Each package contains daily blister packets for a 30-day schedule,

labeled with administration instructions for each sorted medicine, thus improving therapeutic adherence.[114,117] Similar to Amazon, the company is strongly focused on customer service. The service provided has no additional costs beyond the price of the prescription and also collaborates with physicians and insurance providers to gather patient prescriptions and copays, offering automatic refills and 24-hour customer support.[117,118]

Amazon's business strategy is built on three pillars that contribute to its status as one of the most desired online retailers: competitive prices, efficiency, and convenience.[117] Thus, one of the major competitive advantage for Amazon Pharmacy over the other mail-order pharmacies is their customer base. Amazon Prime membership has around 150 million subscribers in the United States, which can provide the company a lot of power when negotiating drug prices with manufacturers and health insurers.[117,119] In addition, the Amazon Prime prescription savings benefit offers Prime members discounts of up to 80% on generic and 40% on branded medications, when paying without insurance coverage, also giving them free-access to two-day shipping.

Currently, the pharmacy supply chain in the United States is extremely complex, having several middlemen contributing to its complexity, which results in price inflation at each stage of the supply chain process.[117] Amazon Pharmacy, as it currently operates, also offers its Prime discounts through a third-party pharmacy benefit manager (PBM). PBMs operate as intermediaries by negotiating rebates with drug manufacturers, providing negligible value to the supply chain.[120,121] Instead, Amazon could use its existing business structure to further disrupt this complex supply chain, by eliminating the middleman and optimizing processes to drive down costs and move discounts directly to patients.[117,120]

Amazon still has much space for improvement in this highly regulated sector. However, measuring what the company has made so far, it seems clear that Amazon is trying to apply its expertise and dominance in the pharmaceutical supply chain as well as in the whole healthcare sector. For instance, in March 2021, Amazon obtained an emergency FDA approval for its SARS-CoV-2 self-testing kit, which became accessible to the U.S. public in June.[122,123]

Currently, it is a common fact that customers are moving toward digital alternatives, thus pressuring conventional companies to stay current. As a result, as it has already started happening, technology companies such as Amazon, Google, Apple or Microsoft will certainly invest substantially on the future of healthcare. If that occurs on a greater level, this companies may have the ability to revolutionize the whole healthcare ecosystem, through the use of remote solutions and digital health.

5. Conclusion

Humankind is facing a period of tremendous technological revolution, which is currently impacting and changing the world at a fast pace. IT plays a relevant role in almost every aspect of human life, from the way people interact with each other to how people interact with machines. Interestingly, this revolution is still at the very beginning, meaning that it will most likely lead to further advances and achievements humans cannot yet predict.

Digital technologies are currently taking the lead in several different industries. The pharmaceutical industry is no exception. Though still in its infancy, some of these technologies have already evolved beyond empty promises and started taking action across the whole medicine's lifecycle. In what concerns R&D, major transformations were observed at the discovery, screening, and clinical development stages, with an extraordinary impact on the innovation productivity. Furthermore, through the application of digital transformation processes, relevant improvements were also observed in manufacturing (pharma 4.0) and supply chain, including logistics, whereas disruptive models of commercial distribution of drug products have been implemented.

Illustrative and tangible examples were described throughout the course of this dissertation. Those were mainly driven by AI-based startups, like Atomwise, Insilico Medicine, AICure, BenevolentAI, and the IT company IBM, while in the supply chain, it comprised the consortium between Merck, IBM, Walmart, KPMG, the blockchain-based startup Modum, and Amazon.

The pharmaceutical sector comprises a complex network of stakeholders, including manufacturers, payers, and patients, thus having an exclusive supply and demand model driven by both clinical and economic interests. This factor makes the pharmaceutical market one of the most competitive in the world. The increased competitiveness translates as an opportunity to highly improve efficiency while reducing costs in R&D; as well as to monitor supply chains securely and transparently, optimizing processes and reducing costs, human mistakes, and fraudulent practices. Thus, providing competitive advantages by allowing further investment in innovation and customer value.

However, the majority of companies in the sector are still lacking an appropriate IT infrastructure or a management mindset that would allow exploiting the full potential embodied by digital transformation. To cope with this revolution, the pharmaceutical industry must find a strategy to overcome its strictly regulated and non-integrated environment while internally investing in IT expertise.

Big tech companies, such as the case of Amazon, Google, Microsoft, and Apple, have an advantage in this matter. Given their position as IT leaders, followed by their vast power around the world, they have already started investing in the healthcare sector. If they compel the pharmaceutical industry into following their lead, it might benefit all stakeholders. Indeed, the key to success has proven to lie in collaboration rather than competition. However, the emergence of these data-driven corporations in the pharmaceutical sector will require further regulation to avoid monopolization and concentration of power in the industry.

6. References

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