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IMPCATIONS OF ADDITIVE MANUFACTURING ON PHARMACEUTICAL LOGISTICS

On the road to Personalized Medicine

Master Thesis

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PREFACE

This report is my graduation thesis of the Master in Science Management of Technology at the Technical University of Delft (The Netherlands). This report shows the research carried out during the months of February to June 2016 at the department of Transport and Logistics of the faculty Technology, Policy and Management. Specially, I need to express my sincerest gratitude to my first supervisor, Ir. M. W. M. Ludema who helped me from the early beginning when I approached to him without topic and completely lost through all the ups and downs and now to the end. Also to my second supervisor, Dr. Z. Roosenboom-Kwee, who showed her interest for the topic from the beginning and was very supportive. And finally to the chief of my committee Prof.dr.ir. L. Tavasszy, who totally helped me with the research methodology and the supply chain modelling.

Apart from the members of my committee, I want to specially mention Drs. B.L. (Bart) van Hulst, from the department of Economics of Technology and Innovation, who was supportive and very helpful providing some useful contacts and an external point of view for my research. Furthermore, of course, my most sincere gratitude to all the experts who I interviewed and all those who, besides their lack of knowledge on the topic, took their time to answer my e-mail and re direct to their colleagues. I want to specially thank Mr. Julian Koster and the people in PCS Pharmaceutical Consultancy services PCS B.V. for putting me in contact with the regulatory experts that I have interviewed for this thesis.

Finally, to my family and friends who listened to my problems and concerns about the thesis and even before that during my stay in the Netherlands. And to Héctor, who no matter what, has stayed by my side all these years.

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SUMMARY

The pharmaceutical field is evolving and getting more and more challenging. Easy targets and compounds have already been discovered and most of the blockbuster's patents are expiring. At the same time, one-fit-all approach of reactive medicine (i.e. the same drugs for all the patients with little variation and aimed to cure the disease not to prevent them) has showed its inefficiency and its shortcomings (PWC, 2012). Many medicines are not effective for that treatment because they do not target the illness's source or they cause severe side effects. Tailor-made medicine or also called personalized medicine offers the opportunity to adapt medicine to each patient's needs. Personalizing refers to adjust to patient's genome and phenotype variations at the same time (body weight, age, gender). Personalized medicine can target genome variations directly with a blood sample or by monitoring body's constants or metabolites concentration to detect when a medication is needed (FDA, 2015; Hamburg & Collins, 2010). The second case has already been developed with smart watches that control heartbeat. On the contrary, devices to continuously check the glucose levels to detect when insulin is necessary (in the case of patients suffering from diabetes disease) are still under development. Personalized medicines based on biomarkers and genetic variations will take longer to bring to the patient.

Furthermore, the biopharmaceutical distribution system and logistics is extremely complex and discontinuous. First of all, at least 2 steps are required to manufacture the solid dosage pill plus quality control and packaging. Secondly, the production model is completely centralized, meaning that the production is carried out in one facility and the products shipped everywhere. This requires a worldwide distribution system with many central and regional warehouses. Such a complex system demands accurate planning and forecasting activities at the same time that demand volatility is really high. Some of the main future challenges that pharmaceutical supply chain faces for the next decade are: move towards a lean production to reduce non-value activities, outsourcing non-core activities and reduction in the final delivery steps to increase responsiveness, reliability and agility. Additionally, increasing visibility and traceability through all the distribution channel is one of the main requirements in the pharmaceutical field due to counterfeiting and quality controls (Dijkstral & Beukema, n.d.; Privett, & Gonsalvez, 2014; Pelzel, 2015). A system of coding with RFIDS or barcodes that track each pill individually would ensure quality and safety for the patient. 3D printing is a strategy not only to track products for example by printing on each pill a barcode plus the company's trademark, but also lowering planning and forecasting activities as production is closer to the customer. In a de centralized production model, customers' demands are easier to take into account and adapt production to their needs (Phillips, 2016). In this way, agility (how the system responds to outside influences), responsiveness (tasks speed) and reliability (outcome's predictability) can be ensured.

3D printing as a production system has gained interest during the last decade. Its applications range from consumable goods (like customizable shavers) to 3D printed food. In the medical field, the most promising applications are dental and prosthetic implants. More recently, due to technological advances and huge investments, 3D printing has started to be considered as a production method for medication. The first drug produced by 3D printing: Spritam® was accepted for commercialization in 2015 (Szczerba, 2015). Due to this recent event and the hype that surrounds 3D printing as a production method for personalized

medicine, the objective of this thesis is to *Provide design alternatives of the pharmaceutical industry supply chain if 3D printing was used to produce personalized medicines and suggest strategic recommendations to encompass those modifications.* The main design objective is: **What would be the pharmaceutical logistics and transportation design if 3D printing was used for drug production?**

This work is oriented towards the design of the pharmaceutical supply chain alternatives if 3D printing is used as a production method. Due to the innovativeness of the topic, firstly a qualitative research is necessary to answer the design objective. This phase will gather information that will be used to define the key design requirements and specifications necessary for the design process. The research is based on the literature and interviews to supply chain experts, pharmaceutical industry, regulatory and 3D printing experts is necessary. The research sub questions that need to be responded refer to how personalized medicines could be produced by 3D printing, how the pharmaceutical supply chain is currently organized and how can the effects of 3D printing be measured. A second phase, which is the main goal of the project, is the design process which is based on an **adaptation of the 5-stage prescriptive model** from Dym, Little, Orwin & Spjut (2004). The stages are 3: problem definition phase where the objectives are clarified and the requirements, the conceptual design where the alternatives are generated and the design communication. The main requirements are printer location, production system, cleaning and cross-contamination, safety, quality, validity, liability and stability. From these requirements, the design alternatives are depictured according to the 3D printer location in the supply chain and then analysed depending on the performance of each supply chain design. From the original 5 stages model, the steps of preliminary and detailed design were skipped because the amount of details required could not be achieved in this project.

4 different supply chain alternatives are generated and a clear and precise design of each of them is shown in chapter 5. The alternatives are developed depending on the 3D printer is positioned in the supply chain as it was found to be the key design specification. Many other alternatives could have been designed just positioning the production point at different points of the supply chain. However, according to the expert opinions, the four suggested positions are the ones that generate more value for the customer. The alternatives are divided according to the production model used: centralized manufacturing like now and three decentralized models: at hospitals, at pharmacies and at patient's home. The results of the alternatives' analysis show that reliability, responsiveness, agility, traceability, flexibility and efficiency increases the closer the printer is to the final customer. Costs, though, decrease in comparison with the current production model but are even lower in the 3D printing centralized manufacturing. However, any conclusions can be drawn regarding costs because apparently they seem to decrease with a 3D production system, but many other aspects such as cost of raw materials, time of production, etc. have to be included to really make a comparison between models. The likelihood of each alternative couldn't be determined with the existing data. Thus, it has been pointed as a future work.

The last step is the design communication provided with an implementation strategy plan. It determines that firstly, devices that help to personalize medicine by continuously check the patient's blood pressure or glucose concentration in the case of diabetic disease patients will open up the landscape for personalized medicine. After some research and development on filaments and inks to produce drugs with existing 3D printing techniques, existing treatments could be personalized. In a third step, small scale

new treatments could be produced by 3D printing; a fourth step would be to mass produce those treatments and finally, in a long-term scenario, medicines will be completely tailor-made manufactured at each patient's home.

Furthermore, the technology adoption discussion in chapter 6 will provide the key necessary breakthroughs that will bring drug 3D printing to the market. And in chapter 7, the conclusions of this research point out that drug 3D printing is still at the market adaptation phase, so to enter the commercialization stage, the key requirements need to be solved: how to determine quality and safety, validate the production process, regulation concerns, expiration dates, counterfeiting, etc. The major breakthroughs to enable mass production of 3D printing are quality and safety measures to validate and standardize the production system and thus, ensure regulation. Secondly, production of value-added products (personalized medicine) and thirdly, mass-production (to manufacture pills at the hospital or pharmacy, how will the demand be fulfilled?). More knowledge transfers through symposiums and conferences and stakeholder involvement through debates will solve many of the last concerns. After the interviews, it was crystal clear that knowledge is not shared between experts because what for some of them were key challenges, for others they weren't. For example, counterfeiting, patenting and expiration dates. At the same time, 3D printing is a value laden technology, this means that the values that surrounds it need to be included in its development not just to avoid rejection and public discontent but also to develop technologies in a more responsible way (Esteban, 2015). Moreover, the complementary technologies: packing systems, new materials, software to design medication and big data to store and analyse all patient's information are necessary to mass produce drugs by 3D printing.

After discussing the supply chain re-design alternatives, the technology adoption rate and stakeholders' involvement, some strategic recommendations are provided to managers. In the short-term, companies are advised to adapt 3D printing in their current supply chain and offered products but not pursuing any radical change. Pharmaceutical corporations will most likely start producing some of their current products that would have a market if personalized, by 3D printing. In a second step, the companies will move towards offering new products that do not exist before the adoption of 3D printing in order to increase product functionality, market responsiveness and customization (Marchese, Crane, & Haley, 2015). However, it will not be until some start-ups commercialize 3D printed drugs, that the big market leaders will move towards mass produce drugs by 3D printing as well and recapping second in the market benefits. The reason behind this strategy is that the risks of bringing a product to the pharmaceutical market are really high and research and development costs as well. However, when the companies finally adopt drug 3D printing, it will represent a new business branch that complements current manufacturing systems. Mainly because it cannot compete with production levels and costs and it offers a new market opportunity: to cover a patients' existing need, to live longer and better.

The scope of this report has been settled covering mostly solid dosage forms production in the western world. Other possible personalized medicines that do not belong to that group have been barely mentioned and the supply chain analysis focuses on production and delivery activities. The focus on western supply chain is because developing countries have a more complex distribution system which is influenced by strong external factors that do not exist in the western economies. The research has concentrated upon solid dosage forms because are the most developed 3D printed drugs; meaning that

more information can be gathered and discussed with the experts. Finally, the supply chain impacts if 3D printing is used as a production method mostly surround make and delivery activities and focusing on them simplifies the analysis.

Another point of uniqueness of this research is the complexity of the pharmaceutical field in comparison with for example the consumable goods market. The reason behind it is that the consequences of not fulfilling quality, efficacy, safety and low costs put the customer's lives at risk which is not the case in other markets. Also, liability has an extreme importance in pharma for the same reason. Furthermore, the value distribution through its supply chain differs from other fields. 3D printing itself fulfils a direct need: substitution of the current methods to improve order fulfilment, reduced returns, reduction in complexity and assembly lines and de centralized spare parts productions. In pharma, the benefits in supply chain's performance are clear but to the end customer are vague unlike in the case of consumable goods (the benefits of a cool 3D printed razor are clear or a customized pair of trainers). **In pharma**, the benefits to the end customer are related to personalizing medicine not to **3D printing** itself; which, in this case, **is just the production method to manufacture tailor-made medicines.**

The main **contribution** of this research are the 4 supply chain designs where 3D printing is used as a production tool and how the make and delivery parts of the supply chain are modified. Also, this thesis provides a first analysis of drug 3D printing technology to produce personalized medicine, determining the key breakthroughs and complementary technologies required to bring the current technology towards the commercialization phase and the managerial strategies for product developers and supply chain planners to do so.

Key words: Supply chain, 3D printing (or additive manufacturing), drugs, personalized medicine, re-design.

Content

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ADR - Adverse Drug Reactions

API – Active Pharmaceutical Ingredient

CTA – Constructive Technology Assessment

DNA - Deoxyribonucleic Acid

FDA- Food and Drug Administration (US regulation system for pharmaceutical products, the equivalent in EU is EMA, The European Medical Agency)

FDM -Fused Deposition Modelling

FHH - Family Health History

GMP- Good Manufacturing Practices

HRA - Health Risk Assessment

IPR – Intellectual Property Rights

KPIs – Key Performance Indicator

PD - PharmacoDinamics

PK – PharmacoKinetics

PMx – Personalized Medicine

RFID – Radio Frequency Identification

RDM – Redistributed Manufacturing

R&D – Research and Development

SC – Supply Chain

SNP - Single Nucleotide Polymorphisms

VSD- Value Sensitive Design

CHAPTER 1. INTRODUCTION

Until now, most medicines are intended to the "average patient" as "one-size-fits-all-approach," which just works for some patients. In order to optimize the current treatments, personalized medicine uses the recently discovered genetic information to fit each medication for a specific patient. What establishes the link between genes and illnesses is called biomarker, which is a general term that includes DNA sequences, the presence or absence of drug receptors and the levels of certain enzymes. Biomarkers will indicate how to treat each patient by himself or herself not by the illnesses that is suffering (FDA, 2015; Hamburg & Collins, 2010; Miller, 2013).

Personalized medicine is a completely disruptive revolution and will necessitate an accurate valuation of its opportunities and challenges. Pharmaceutical leaders are already researching this new type of medicines as can be seen in their webpages. The most notable ones are TEVA pharmaceuticals, Amgen, Roche, GSK, etc. Taylor made medicines represents a big opportunity for pharmaceutical companies to restore their position as market leaders with high profits. The future prospections are less favourable with smaller markets and reduction of revenues, as blockbuster drug patents are expiring (PWC, 2012). Although many pharmaceutical and biotech companies have already based their drug research and development programs in biomarkers; most of them are in their infancy (FDA, 2015).

After seeing the customer need for this type of medicine and the occasion that it represents for pharmaceutical companies, it would be very interesting to study how medical treatment could be achieved. One possibility that has been considered lately by many researchers and pharmaceutical companies is to use 3D printing technology to adapt medications to each patient's needs. The last two decades, 3D printers have disrupted the production of everything that we know. Is now the time for the pharmaceutical industry? By producing drugs with a 3D printer, a local and highly specialized production would be reached and as the manufacturers could print on demand, the large volume of finished products stored in enormous warehouses would most probably disappear (Robinson, 2015).

But, in which point of the supply chain will drugs be produced? Many possibilities do exist and depending on which is chosen, the design of the supply chain will be completely different. For this reason, whether the current model will remain unchanged or perhaps totally transformed is matter of further exploration in this thesis (Meyer, 2015). First of all, in chapter 2 the research problem that this thesis tries to answer is further explained and from there, the design objectives and questions are derived. Additionally, the study relevance, the scope and the framework used in the whole research are explained and the research methodology. The results are divided into chapter 3 and 4 which are the problem exploration phase. Chapter 5 links the ideas from the previous chapters with the results obtained from the interviews and develops the design requirements and specifications to re-design the pharmaceutical supply chain. In chapter 6, further discussion about the technology is provided preparing the ground for chapter 7, conclusions. The results in chapter 5 will bring to light the design requirements and challenges that drug 3D printing represents and according to printer's location, the supply chain performance would be analysed to compare between alternatives. The main idea of that was to assess which alternative was more likely to become a reality but, as it would be explained later, that is a limitation of my research and would require future work. In the discussion, chapter 6, further research on the technology adoption and

corporate responsibility will provide insights on the stage of adoption of drug 3D printing. Linking them with the requirements to bring the technology to mass production, will deliver a technology implementation plan and further strategic recommendations. The delivery of this investigation is the provision of 4 different supply chain designs where 3D printing is used as a production method plus strategic recommendations to pharmaceutical leaders and supply chain managers of how 3D could impact on their logistics and transport system.

Figure 1 shows the design approach. As previously explained, preceding the designing part, a research and design methodology section (chapter 2) where the objectives, the problem itself and the research methodology are explained to define the goals of the design. A second phase is the problem exploration which establishes the design requirements and specification. The third phase is the design process itself. The fourth phase is the discussion where other aspects of the technology need to be considered to develop the implementation plan of the supply chain re-design alternatives and provide managers with recommendations. And finally, the conclusion where the results of the research are used to provide strategic recommendations to stakeholders and managers, reflection regarding this investigation (its scope, pharmaceutical field uniqueness, scientific responsibility, etc.) and the scientific and managerial contributions of this research.

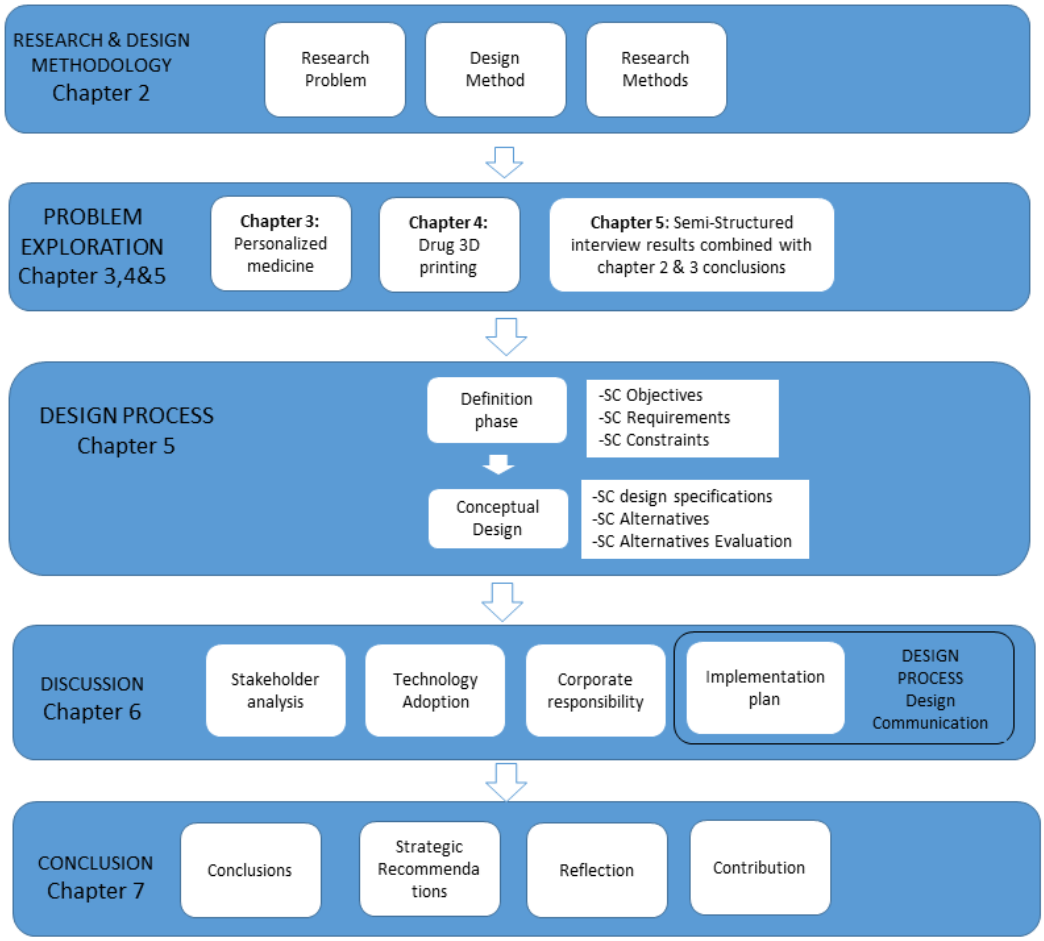

Figure 1 Research approach. Source: this project

CHAPTER 2. RESEARCH & DESIGN METHODOLOGY

This section shows the design methodology used to determine each of the supply chain re-design alternatives. To do so, a pure research part is previously needed to explore 3D printing technology and apply it to drugs. For this reason, a part from the design methodology, in this chapter a detailed pure research approach is explained. The chapter starts with an explanation of the research problem to understand the need for this research. After defining the problem, the design objectives are established. Afterwards, the research and design methods are explained in detail. Finally, the scope and relevance define the limits of the designs applicability and the importance for the society. Figure 2 shows where chapter 2 is positioned in the whole report structure. In the research and design section 2.7 a more detailed scheme of the whole thesis is provided.

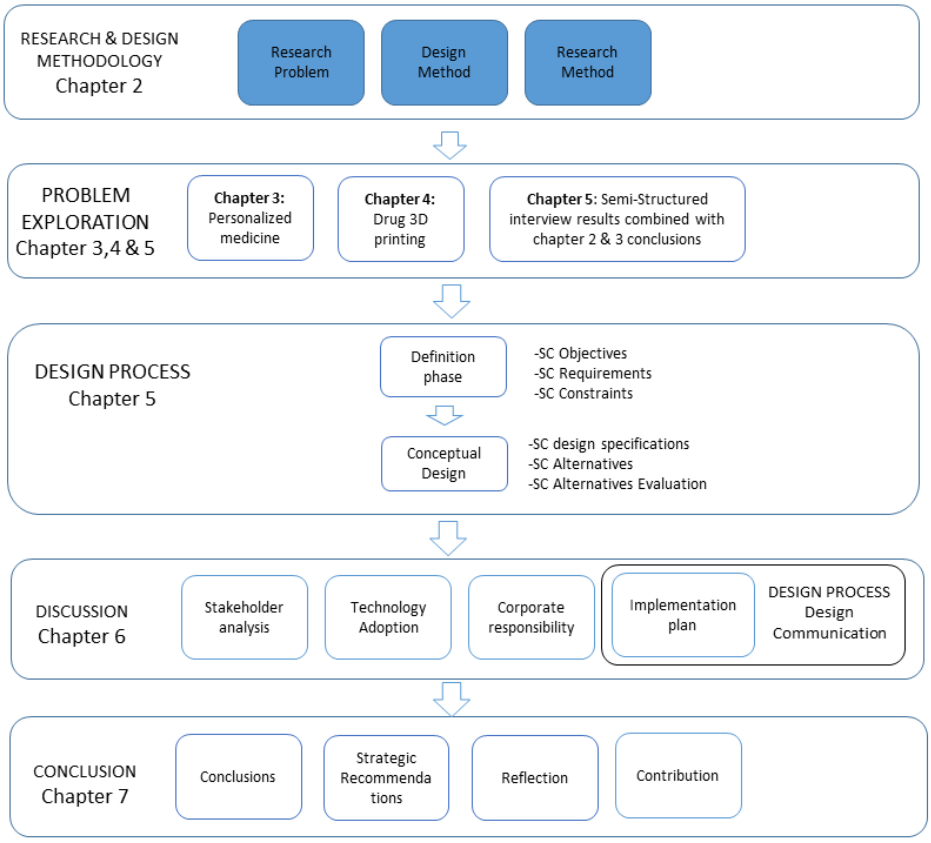

Figure 2 Position of Chapter 2 in the whole research framework. Source: this project

2.1 Research problem

The research problem refers to a difficult question that needs an answer. In this sub section the current pharmaceutical position and supply chain are explained in detail to define what the research problem is.

Pharmaceutical field actual position

The pharmaceutical industry comprises a well-defined grouping of processes, operations and organizations that collaborate in order to discover, develop and produce medicines. The main players in the pharmaceutical industry include: global research and development-based multinationals, huge

generic producers and site manufacturing companies. Besides, there are the contract manufacturers who produce either production intermediates, active pharmaceutical ingredients (API) or final products for other enterprises. And finally, small biotechnology companies characterized for being new start-ups with lower production capacity (Shah, 2004; Esteban, 2016).

The global pharmaceutical market is exponentially growing because while the population rises, ages and turns out to be more sedentary. Moreover, "the life span is also widening; leading to more cases of dementia and age-related diseases" (Esteban, 2016, p.2). Furthermore, there's been an upsurge in the incidence of infectious diseases as some infections have developed drug-resistance at the same time that the movement of humans and transportation goods between countries has increased. To add insult to injury, over the past decades, new microbes and viruses like HIV and MRSA have emerged. These events have been translated towards a prominent raise in medication need (PWC, 2012; Esteban, 2016).

Additionally, healthcare payers are forcing new cost restrictions on producers and scrutinize the medicine's value more thoughtfully. In addition, both US Food and Drug Administration (FDA) and European Medicine Agency (EMA) are getting more severe regarding visibility, compliance and pharmacovigilance. This fact imposes the companies to control ingredients' production standards and track the medicines more cautiously after introducing them in the markets (Deloitte, 2014; Esteban, 2016). Furthermore, research and development programs are less fruitful in terms of obtaining new drugs because many 'easy' targets have already been developed so pharmaceutical industry is facing **drug shortages**. The main causes of this problem are the current manufacturing model and the number of suppliers. Batch wise manufacturing is still the production method for the pharmaceutical industry. Despite all the advantages that continuous production has over batch, pharmaceutical companies are still producing by batch which causes loses in productivity in terms of supply chain shortages and quality controlling. This is because setting up a batch is time consuming and many steps in the production process are disconnected. Moreover, pharmaceutical companies rely on few suppliers and that causes loses in terms of adapting to demand changes (Yeston, 2016; Keeling, Lösch, & Schrader, 2010).

Another actual fact is that pharmaceutical companies are accused of **charging too much for the drugs** and that only those drugs that can profit from are produced. Here there's an ethical dilemma because from one side any pharmaceutical company is a business and for that reason it needs to make profit; and from the other side, not only the lucrative medicines should be produced to ensure society's welfare. Despite the public's vision of pharmaceutical's position, almost every leading pharmaceutical company participates in funding programs that enhance the research and development of those orphan drugs (those that affect to a small segment of the population and at the first sight, they could be considered too expensive to invest on). Also, many regulatory benefits do exist as well to enhance the production of those less lucrative drugs. Furthermore, most of the big pharmaceutical companies are involved in charities and programs to help society. So, in the end this ethic issue is partially solved. The reason why pharmaceutical companies tend to concentrate on most lucrative diseases is because drug research and development is highly expensive: usually a drug can take around 12 years to reach the market with a cost of £1.15bn (Thomas, 2016). Drug research and development is resource intensive as the process involves 8 stages: pre-discovery stage (in which scientists identify a target to treat a specific disease and it takes 2 years and costs $10m); the following step is the pre-clinical testing (first studies to test the drug's toxicity), then the

clinical trials (in which around a 1000 of patients are tested) in which only 70% of the compounds get through. The main issue in this point of the development process is the requirement to produce high quality pure compounds in enough quantities to fulfil the clinical trials. If the compound goes through, they are submitted for licensing approval and then commercialized. The numbers establish that only **1 compound in 5000 drug candidates gets to the market** (Kraljevic, Stambrook, & Pavelic, 2004).

"Another difficult front are the **current market conditions**: stricter price controls and the expiration of many patents, many of them from blockbusters" (Esteban, 2016, p. 19). To illustrate this just look at some figures: the multinational company Eli Lilly dropped its net profits by 20% once Prozac came off patent. In AstraZeneca's case, the lost was a 34% of their sales when Losec came off patent in 2001(Shah, N., 2004). Both Prozac and Losec were the most profitable blockbusters that each company had until they went off patent (Esteban, 2016).

The explained situation is the motive why companies are pushing for **diversification** of their therapeutic and business areas or expanding towards new locations such as entering in new emerging markets (Rusu, Kuokkanen, & Heier, 2011). Many other strategies have been suggested to reduce the effort and cost that the drug development process requires, for example using digital sensors to collect data and follow the treatment. Another option is drug repurposing, to use a drug for another disease that is not the one that was researched for (Thomas, 2016). And the most innovative approach is to develop personalized medicine which will be explained in section 3.3.

Market analysis: Western pharmaceutical industry

According to WHO (World Health Organization) estimations, the value of the global pharmaceutical market is around US$300 billion a year with prospections to increase 100 billion of $US in the upcoming three years. The main pharmaceutical companies are located between US and Europe mainly: six of them are located in the US and four in Europe. The predictions show that a part from EU and US, Canada, South America and Japan will be providing the 85% of the total pharmaceutical market during the whole 21st century (WHO, 2016).

Regarding the biopharmaceutical distribution, the supply chain organization is extremely complex and fragmented. According to numbers from the US market, only 6% of around 140,000 prescriptions are directly served from the manufacturer to the client. This implies that to serve the remaining 94% the distribution channel needs to reach them all; increasing the complexity of the whole distribution network. This complexity increases with all the countries in the world included in the network (Rossetti, Handfield, & Dooley, 2011).

Pharmaceutical supply chain

Before starting analysing the current pharmaceutical supply chain, first of all an accurate definition of what's the company's supply chain is provided: a supply chain is understood as an united system of related business processes with the aim of: "(1) acquire raw materials and parts; (2) transform these into finished products; (3) add value to these products; (4) distribute and promote these products to either retailers or customers; and (5) facilitate information exchange among various business entities (e.g. suppliers, manufacturers, distributors, third-party logistics providers, and retailers)" (Min, & Zhou, 2002, p. 231).

More specifically, it can be described as "the integration of key business processes from end-users through original suppliers that provide products, services and information at the same time that adds value for customers and other stakeholders" (Min, & Zhou, 2002, p. 231).

By checking the effects on the pharmaceutical supply chain of this group of businesses, the producers of value for the customer will be taken into account. Those activities are classified according to their position versus the production process: the ones located upstream (planners, suppliers) and downstream (customers, logistics and packing) (Mentzer et al., 2001; Esteban, 2016). Specifically, the **perspective of my research** focuses in the production and downstream of the supply chain. This is because the position of the printer (the production stage in this case) is what will determine the modifications in the logistics. As it will be analysed in the following sections, the printer could be located as a complement to the current manufacturing process or downwards in the supply chain.

Scheme of the actual supply chain

A representative pharmaceutical supply chain comprises the following nodes (figure 3): raw materials sourcing, manufacturing (divided into first and second production steps); distribution centres or warehouses (global and regional); wholesalers; retailers (hospitals, clinics and pharmacies) and patients (customers) (Shah, N., 2004).

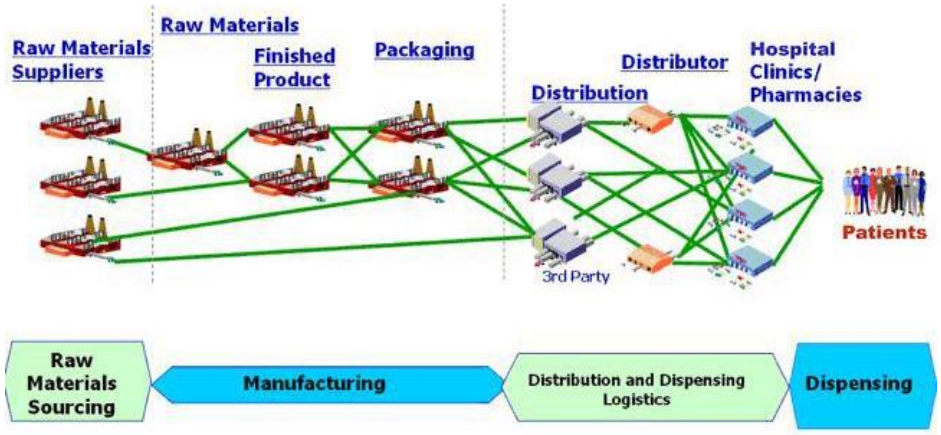

Figure 3 Pharmaceutical supply chain scheme. Source: (Rocky Mountain Technical Marketing, Inc., n.d.)

The **first production step** is accountable for the manufacture of the API. This consists of either several chemical synthesis and separation steps to form the complex molecules, or in the case of biochemical processes, fermentation, product recovery and purification. Thus, the manufacturing process is characterized by long task processing times, with many multistage processes and considerable inventories. Additionally, the material needs to pass a quality check before being approved to transport and sell. Therefore, both quality control and inventories introduce delays into the system. Following this step, there is the **secondary production step** where the excipient is added to the API created before and then, the entire product is packed and stored. There are often many more secondary manufacturing sites spread to supply regions far from the manufacturing sites. Another point is transportation. To transport products between sites is essential in any supply chain and in this case, it takes from 1 to 2 weeks by ship and one or two days if it's by air: however, this mode is the least common.

Most pharmaceutical companies assemble the API in the company's manufacture facility by mixing different raw materials provided by various sources. Then, the API is mixed with excipients in the secondary manufacturing stage, as already mentioned, and then formulated in the final product. Due to these different stages of the drug manufacturing, the process takes 12 months plus large inventories situated in different intermediate stages. As mentioned in the introduction of this section, the reduction of this inefficiency is one of the main reasons to strive for continuous manufacturing at the same time of producing the drug tablet in one single process (Yeston, 2016).

Dispensing is carried by **wholesalers** who by forming an oligopoly, control about 80% of demand flows (Shah, N., 2004). Wholesalers either sell to retailers (pharmacies and hospitals) and those to the patients; or to another wholesaler. However, there is another channel of distribution that goes from manufacturers directly to pharmacies and hospitals and to the patients too (direct channels through the internet) but is less exploited than the previously explained (Müller, Pöpke, Urbat, Zeier, & Plattner, 2009).

Regarding the European pharmaceutical industry, approximately each year around 30 billion packages are produced within Europe. Half of them are drugs available on prescription and the other half are over-the-counter products[1]. According to the calculations that Müller, J. et al., 2009, made, the European supply chain is formed by "2,211 manufacturers, 50,400 wholesalers, and 142,000 retailers" (Müller, J., et al. 2009, p.45). That gives an average production rate of 18.638 packages of drugs per day per producer.

Trends in the supply chain

The last hundreds of years, having an inimitable product with a long life cycle was the winning horse. Nonetheless, nowadays the life cycle of the products is getting shorter and shorter and products are more customer-driven; thus, the supply chains need to be more flexible and **adaptable**. A more transparent and responsible supply chain is vital (Longman, 2015).

Due to the price difference between manufacturers and the high development and production costs, pharmaceutical products have an incentive to be counterfeited. A strategy to avoid that is to increase transparency and traceability in the supply chain (King, & Zhang, 2007).

Furthermore, the most successful method to increase **visibility and transparency** consists in tracking the raw materials and the final products through all the supply chain using sensors. With this method, any abnormalities would be detected and also, insight regarding manufacturing quality and delivery timing would be gathered. Additionally, the increase in visibility covers two other industry needs: security and risk management (Keskin, 2015; Longman, 2015).

The last trend is **redistributed manufacturing** (RDM). Pharmaceutical's current production model is centralized meaning that all production takes place in the same location. This model is threatened by factors like innovation, economical risks and climate change. By contrast, Redistributed Manufacturing (RDM) is a decentralized production model in which production is moved closer to the customer providing a faster response and lowering production costs (transport, energy and raw materials). Consequently, increasing responsibility, lowering the risks and reducing the ecological impact. RDM is perfect for the

[1] *Over-the-counter products* are drugs sold directly to customers without prescription.

Pharmaceutical sector as it reduces lead time and long supply chains. Additive manufacturing is the production system to enable RDM as it enables a higher quality, product complexity and more variability between products (University of Sussex., n.d.; Phillips, 2016).

Trends in market-product characteristics

Product market strategy explains how a company by positioning its products in the market gains and maintains its competitive advantage. This concept involves questions such as: what strategy should they adopt? (differentiation, leadership), what position to adopt against competitors? when is the best moment to enter the market, which products to sell? which are the targeted customers? (Zott, & Amit, 2008).

In the case of pharmaceuticals, the key strategic characteristics are **demand proximity, regulations and government intervention, supply chain structure and innovation**. The pharmaceutical industry is characterized by highly R&D intensive as its business model is strictly based on developing new products and services to their customers. Also, the trends establish that due to the nature of their products and the current high transportation costs, the production would get closer to customers to minimize those and also to fit customers' needs (Manyika et al., 2012). Drug 3D printing will demonstrate its benefits in these terms (section 5.3 and 5.4).

New Supply chain structure

The "good times" for pharmaceutical companies are over, companies need to adapt to remain competitive in the market. Also, policymakers and governments aim to reduce healthcare costs and the clear way to achive it is putting pressure on big pharmaceutical companies to lower the costs of medicines. In order to adapt to the changing paradigm, pharmaceutcial companies would need to focus more on direct sales channels. This strategic decision will reduce their profit margins, increase the supply chain's agility, responsiveness and push the medicines' to market. In order to do this, companies will deliver directly to pharmacies and hospitals at the first stage, but in the long run the aim is to fulfill customers' needs directly (see figure 4) (Dijkstral & Beukema, n.d.). So, pharmaceutical companies need to focus on increasing efficiency to maintain their margins and find how to bring the production or supply chain closer to the customer (Rossetti, Handfield, & Dooley, 2011).

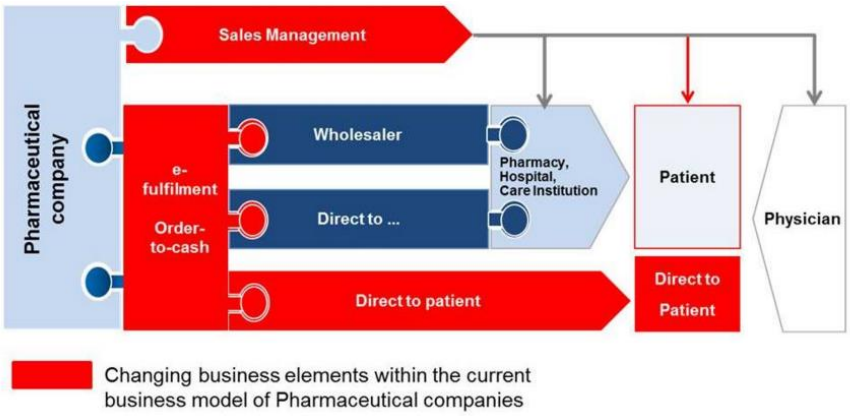

Figure 4 Pharmaceutical current and future distribution channels. Source: (Dijkstral & Beukema, n.d.)

In Western countries, the current distribution model would change to adapt to new needs. Some of the changes imply giving more importance to less traditional selling points like the internet and mail order which have been adopted lately with great success. Furthermore, mostly in the US, recently big chains specialized in serving pharmaceutical products such as Walgreens have risen and by gaining importance, their bargaining power regarding medicines' cost is increasing. The landscape in emerging countries is slightly different; however, its analysis goes beyond the scope of this thesis (Dijkstral & Beukema, n.d.).

Moreover, hospitals and pharmacy chains are moving from buying monthly to wholesalers towards negotiating contracts directly with pharmaceutical companies. Skipping one player of the supply chain, these large purchasers buy drugs at lower prices. Currently, around 30% of the total drugs are purchased through this channel. This approach not only lowers the prices, it also affects supply chain's fluidity and agility due to fluctuations in demand and uncertainty (Dijkstral & Beukema, n.d.).

The strategy that pharmaceutical companies would strive for the upcoming years would differ: some companies will focus on developing more cost efficient supply chains by optimizing their distribution models. For others, the key would be to develop a more agile and responsible distribution system (Dijkstral & Beukema, n.d.).

Strategies to revitalize the pharmaceutical market:

1. **Adopt a tailored business model:** a model of low-margin products, high inventory levels and service levels is not suitable. Pharmaceutical companies need to move towards individual supply chains specialized in a precise product, market and customer segment. Many pharmaceutical companies are adapting to this new business model, one clear example of it is when Pfizer spun-off one branch of its business and J&J bought it (Rossetti, Handfield, & Dooley, 2011). This is not an isolated case, it has becoming a trend in the pharmaceutical field to focus only in the business area that the company has capabilities and strengths to develop.
2. **Add flexibility to product design and packaging.** So, a personalized pill could be shipped to different regions effectively. Or the company can pack the drugs when the order comes in reducing inventory levels and complexity (so-called postponement strategy). At the same time that manufacturers make sure that the products arrive to their customers when they need them (Rossetti, Handfield, & Dooley, 2011).
3. **Reconfigure the supply chain footprint.** Average industry asset utilization is around 40 percent due to large-scale factories with low productivity. Restructuring the supply chain footprint would enable companies to become more efficient and increase their competitive advantage.
    a. **Product life-cycle model**: production can be shifted to other plants with lower costs.
    b. **Technological model**: around new production or innovative practices, new manufacturing centres are created.
    c. **Geographic model:** depending on local demand, plants are located in one place or another.
    d. **Complexity model:** production plants are divided into high and low volumes and complexity products depending on resources, demand, competition and pricing opportunities.

e. **Product and therapeutic model:** some products or areas share R&D, manufacturing, strategic marketing, etc.

4. **Improve planning capabilities:** to remain competitive, firms require an accurate planning. This guides the business in managing inventory, returns liabilities and sales drop. Companies with optimized planning processes have "lower inventory levels, supply chain volatility and production and logistic costs and supply chain resilience (the ability of the system to return to the original state or move to a new more desirable state)" (Ponis, & Koronis, 2012; p.924) (Ehrhardt, Hutchens, &Higgins, 2012). Until now the tendency has been to move inventory upwards the chain; instead keeping it in the wholesalers, it is moved towards manufacturers to ensure that demand is covered (Rossetti, Handfield, & Dooley, 2011).

Other strategies involve **linking pharmaceuticals and diagnostics**; in such alternative the success of both companies is related. The collaboration between them will bring drugs to the market that better suit customers' needs. Another approach will be to shift towards a customer-centric healthcare in which pharmaceutical companies provide preventive medicine and non-prescription drugs. And the last approach involves pharma focusing on therapeutic areas, the ones that have greatest chance for technical and profitmaking success. This strategy involves partnering to build up a specific business area at the same time of selling or buying others (Kandybin & Genova, 2012).

Future challenges

Nowadays, with the challenging situation that pharmaceutical companies are facing, supply chain excellence matters more than ever. After analysing which are the trends, performance indicators and the future challenges, in this section the future challenges that the supply chain will encounter and adapt to will be scrutinized. The information gathered is summarized in table 1 in which each challenge is organized according to its affects on planning activities, sourcing, making or distribution. Then, for each challenge the current situation is explained and the expected future. And in the fifth column, the effect that 3D printing would have on this challenge it's pointed.

Table 1 Pharmaceutical Supply Chain Challenges. Adapted from: (Dijkstral & Beukema, n.d.; Privett, & Gonsalvez, 2014; Pelzel, 2015).

	CHALLENGES	CURRENT SITUATION	FUTURE SITUATION	3D PRINTING
PLAN	**Current Business model**	Indirect marketing and sales mostly	Direct marketing and sales.	Production and sale at the same location
	Cost reduction	Margin driven	Cost driven	High costs in production but lower in distribution.
	Collaboration & Partnerships	Individualistic supply chains	Collaborative supply chains also to lower R&D costs.	No influence
SOURCE	**Mergers & Acquisition**	Many suppliers	Merge to have a stronger position in the market	No influence
MAKE	**Efficiency**	Lower costs and reduce	Move towards lean production to reduce non-value activities.	**Agile** production able to adapt to changes in demand.

		double activities		**Lean** production, less material inputs.
DELIVERY	**Responsiveness**	Push driven	Pull driven	Pull driven
	Inventory management	Semi-automated stock counts and inventory levels. Keeping large levels of stock to meet regulatory requirements and elude stock-outs.	Rationalization and out-source non-core activities.	Reduction in: -Inventories required to support customers' demand -Lead time -Dependency on forecast accuracy -Small inventory can be easily produced. - Product expiration
	Lack of coordination between linkages in the supply chain	Demand information is not shared through all supply chain.	Need for more coordination to avoid effort duplication and not optimal usage of resources and supply chain underperformance.	Reduction of supply chain linkages.
	Warehouse management	Poor storage and large quantity of immobilized resources		Small storage
	Visibility and information sharing	Black box	Information transparency	Increase in supply chain transparency
	Final Mile delivery	Mass production	Product/market/customer choice	Reduce it. There are at least 2 steps that could be avoided.
	e-commerce	Manual and indirect	Online commerce	3D printing could be used like generics now, order online and get the medicine directly home.

Linking supply chain challenges and the strategies to revitalize the market, 3D printing of drugs offers a tailored business model (the supply chain is specialized for personalized 3D printed products) and flexibility to both production and distribution is increased. Also, the supply chain becomes more efficient: less inventory, smaller warehouses and reduction in supply chain linkages. Furthermore, 3D printing moves the production system towards a more lean-agile production: lower costs at the same time that double activities are eliminated. And finally, 3D printing raises visibility and information sharing throughout the whole supply chain. In chapter 5, the analysis of the different supply chain alternatives will conclude in the same terms as in this section.

Trends in the pharmaceutical field in the next 10 to 15 years

The list of trends is narrowed down to the ones that could modify the current supply chain of the pharmaceutical companies. These possible paths are: cross-industry collaboration, emerging markets, increase in visibility and traceability, outsourcing and logistics cooperation.

After an accurate and in depth analysis of each trend (appendix PART A), **personalized medicine** has resulted the most promising and interesting in terms of innovativeness and impact. In fact, personalized medicine will involve radical changes in the pharmaceutical industry and medical practice but its effects will spread towards many aspects of society; mostly benefiting the individual patient (Ginsburg, & Willard, 2009). For this reason plus the researcher's own interests, the topic captured the attention of this thesis. In chapter 3 personalized medicine is studied in depth.

Section Conclusions

The decisions that pharmaceutical companies will make between now and the end of 2020, will narrow down the occasions that companies could capitalize upon during the next decade. There are many new technologies that are entering the market with numerous possible applications, alternatives to the known drugs are appearing, customers are getting more demanding, different agencies are developing new regulations, and so on. A question that this thesis is asking is "How will 3D printing fit in this scheme?

3D printing applied to the medical field has grown interest since the beginning of this century, but more recently, due to technological advances and huge investments, 3D printing has started to be considered as a production method for medication. As representatives of the FDA established: with 3D printing we will "boldly go where no drug has gone before" (GMP Issues for 3D Printed Pills Resolved But Is It Really a Big Deal, 2015).

It is of great interest why after all the awareness surrounding 3D printing and its application in medical production, there aren't any drug 3D printed in the market yet. It is true that FDA just accepted the first 3D printed drug, SPRITAM® produced by an American company called Aprecia Pharmaceuticals. Although it represents a big step, any drug hasn't been commercialized yet. Furthermore, in the case that 3D printing was used to produce drugs, what would be the logistics implications to produce pharmaceuticals by 3D printing? Will all the supply chain change? The impacts of 3D printing in the market are of extreme importance because the business itself can change completely. The implications of these are broth: financially, logistics, strategic, etc. Therefore, the future of the pharmaceutical companies is highly uncertain and variable.

Thus, in this thesis, by analysing the implications that producing drugs by 3D printing would have on the supply chain, the changes in the overall pharmaceutical business are clearly depictured.

2.2 Design Method

The importance behind using a design method is to provide a methodological approach to solve problems which are defined by certain objectives and constraints. Also, it maintains objectivity and increases the probabilities of success (King, 2015).

For the pharmaceutical supply chain re design process, the model to be used is an adaptation of the **5-stage prescriptive model** described in Dym, Little, Orwin & Spjut, 2004. With this model, the design objectives will lead to design requirements and constraints that will determine the supply chain design alternatives. The model used in this case consists of 3 stages: **problem definition phase, conceptual design** and **design communication.** The original model has two more stages between the conceptual design and the final design communication stage: the preliminary design and the detailed design. In the preliminary design, the first design idea is embodied with the performance specifications and the operating requirements. The detailed design stage develops a more complete design including the specifications and requirements defined in the previous stage. As it will be highlighted in the design phase (section 5.3) the amount of detail required already in the preliminary design could not be achieved and that's the reason why these two stages were skipped.

Why this model?

According to Avramenko and Kraslawski (2008), the simplest design process has 3 stages: generation (states what need to be shaped), evaluation (the design is tested against the principles that the designer has set) and communication (the design is explained). However, an extended and widely accepted model such as the proposed by Dym and Little provides a more detailed design process. The model firstly, incorporates more steps in the design process and secondly, each stage describes in depth which design tasks must be performed (Dym et al., 2004; Avramenko, & Kraslawski, 2008). The two extra stages that Dym and Little propose (preliminary and detailed design) haven't been included in the design model used in this research. Thus, it could mean that a simpler design procedure would have been enough at this stage of the research. However, by using this model, the future's work path is already established and the results of this design approach are more generalizable.

The main limitations of Dym and Little's model are: many correct solutions, conflicting specifications, possibility of using incorrect data and need for trade-offs (Keith, 2005). In this specific case, the encountered limitation was the numerous possible supply chain re-design possibilities, but non conflicting specifications nor trade-offs were necessary.

However, as already mentioned, Dym and Little's model is the most accurate and widely accepted design model and that's the main reason why it was used in this thesis.

Figure 5 develops in detail each of the design steps that will be explained in the following sub sections. Next to the design phase it is specified to which Dym and Little model stage belongs and **the research question** or **design objective** is fulfilled.

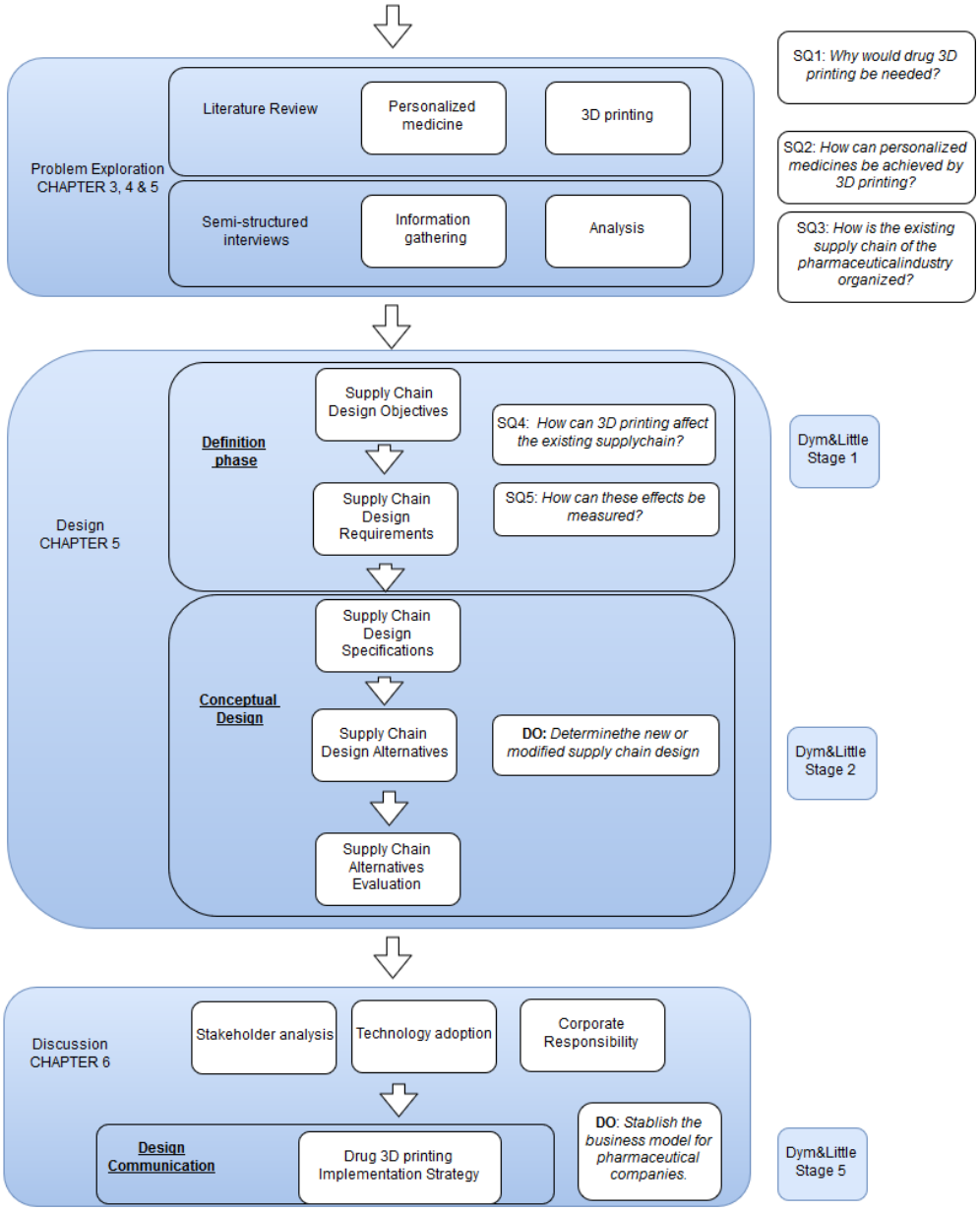

Figure 5 Design process in detail. Source: this project

The first stage of the design process, the problem definition phase, is research oriented towards establishing the design objectives that will lead to the design requirements and design specifications. The requirements and specifications are needed to determine the supply chain design alternatives. In the **problem definition phase** the research sub questions (SQ) answered are: *How can 3D printing affect the existing supply chain?* and *How can these effects be measured?* The second stage, the **conceptual design**, leaves research and moves towards designing the different supply chain alternatives. After obtaining the different alternatives, each is evaluated in terms of performance. Finally, the **design communication** provides the strategy to implement the design (it is included in the discussion section of the report). The design objectives (DO) fulfilled with these two stages are: *Determine the new or modified supply chain design* and *Stablish the business model for pharmaceutical companies*. As explained in the first paragraph

of this sub section, the third and fourth stages of Dym and Little's model are not included in the design methodology of this thesis.

2.2.1 Problem Definition phase

The first stage, the problem definition phase, consists in clarifying the **design objectives** and establishing the SC **requirements**. In order to obtain the design requirements, the literature and the expert data will be used.

Following from the research problem from sub section 2.1, the main design objective is to:

Provide design alternatives of the pharmaceutical industry supply chain if 3D printing was used to produce personalized medicines.

As a sub-objective: **Provide strategic recommendations to encompass those supply chain modifications.**

To reach the main goal, the following sub-goals need to be addressed:

- Determine the new or modified supply chain design.
- Determine the business model for pharmaceutical companies.

After assessing the implications of 3D printing on the pharmaceutical supply chain, a model will be provided with the most probable future case alternatives that can develop after 3D printing would be used as a production method in the pharmaceutical companies.

In the end, from the possible case alternatives, it could be assessed how the company's logistics and transportation will most likely look like and then, provide recommendations to supply chain and product managers of the pharmaceutical companies of how to adapt and be prepared for this change.

2.2.2 Conceptual Design

The second step, the conceptual design, entails determining the **supply chain design specifications and constraints** and from those, generating different alternatives.

The design specifications were **validated** also by supply chain and 3D printing experts. To do so, the specifications were sent to the researchers and they commented on them. The feedback was included and improved them.

SCOR Model

After establishing that the model alternatives will be assessed in terms of supply chain's performance (5.3), the best model to do so was the SCOR model which measures the total supply chain's performance.

The supply chain operations reference (SCOR) model is a strategic planning tool that simplifies the complexity surrounding supply chain management and aims to improve the alignment between the supply chain performance and the marketplace. The model enables managers to analyse, optimize and communicate supply chain management practices. Nowadays, SCOR has become an industrial standard and is rooted in all industrial practices (Huan, Sheoran, & Wang, 2004).

SCOR model is used in this report to depicture and understand, first the current pharmaceutical supply chain and then the future re-design alternatives. With SCOR, the process is explained in increasing levels of detail; first an overview of the entire process is provided and then it is divided into elements, tasks and activities (see figure 6).

SCOR model combines the core processes (level 1 metrics) with the process categories (level 2 metrics) enabling the modelling of many different supply chain configurations. Furthermore, there's a third level of the SCOR model (element level) which the process categories are divided on the individual process elements (Fronia, Brunner, & Nyhuis, 2009). In this report, the SCOR level 1 and 2 are used because the detail that level 3 provides doesn't help comparing the different alternatives. More details are provided in section 5.3.2.

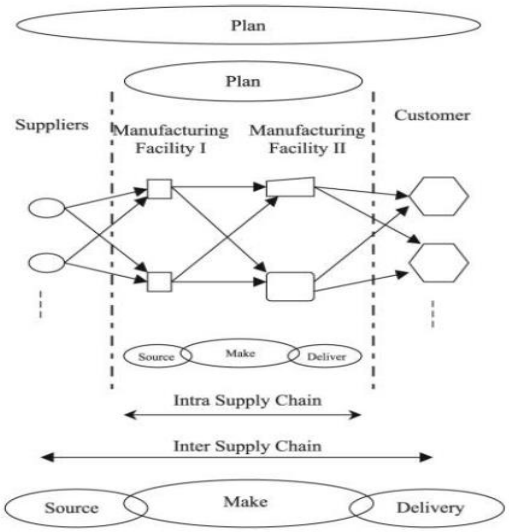

Figure 6 SCOR Model. Source: (Huan, Sheoran, & Wang, 2004).

Why choosing SCOR model?

The reason behind choosing this qualitative method is due to its great explanatory power and clarity. With few signs, a clear picture of each supply chain node and the interactions between them are explained. So, for the purpose of the design which was to show a first idea of how the supply chain would be re-designed, this model was a clear match. Furthermore, SCOR is a model that clearly states the SC re-organization in case of changing the 3D printer position and how manufacturing, distribution and planning activities are affected.

SCOR focuses on measuring the performance of the **procurement, manufacturing and logistics activities** which belong to the operational level of the business process management. Consequently, R&D, marketing, customer support and sales are not included in SCOR (Ludema, 2015). Achieving the goals at the operational level leads to meet the tactical objectives which in turn primes to achieve the results specified at the strategic level (company strategic goals mainly). Consequently, although many other aspects of firm's performance are not included at the SCOR level, it represents the first step to achieve those (Gunasekaran, Patel & McGaughey, 2004).

In order to integrate and maximize supply chain's effectiveness and efficiency, the indicators used are the performance measures. Also, they can be used to compare between systems (or in this case, alternatives), which is the main interest of this research (Gunasekaran et al., 2004).

A part from the fact that SCOR only refers to the operational level of a firm's performance, it has other limitations:

- Does not prioritize the performance measures. Some tools have been suggested to overcome this limitation such as Analytic Hierarchy Processing, but not all the researchers accept it as the best approach to prioritize the measures.
- Performance indicators are considered as static rather than dynamic.
- More international supply chain performance benchmarks to compare supply chains across countries and market sectors.
- Lack of connection with strategy
- Focus on cost indicators
- Insufficient focus on customers and competitors (Shepherd, & Günter, 2010)

Lack of focus on customers and competitors is not a limitation for the SCOR model developed for the pharmaceutical supply chain re-designs because customers' needs are already taken into consideration in terms of personalized medicines and competitors are non-existent at the moment. Lack of strategy connexion is not a limitation because the industry's strategy to move towards personalized medicine has been considered in the first place. And the other listed limitations would be applicable in a more detailed version of SCOR, in this design stage they do not represent any problem. The specific limitations will be discussed in the reflection section in chapter 7.

Supply Chain alternatives

In order to generate the supply chain design alternatives, firstly the design specifications and constraints are determined from the problem exploration phase (literature review plus semi structured interviews to field experts). After that, a SCOR model of each probable future supply chain alternative would be drawn and analysed. In the end, the models will be used to give strategic recommendations to pharmaceutical leaders but also to supply chain managers about the impact that 3D printing of medicines could have on their logistics and transport system.

After each alternative is depictured, the drafts are tested and evaluated and the feedback is incorporated.

In order to **validate** the design, the supply chain experts were asked for feedback in a formal design review. The design alternatives were presented to two experts, one that was already interviewed and another completely new, and the implications of the designs were discussed and assessed. The two experts were: Sam Onukuri, who hasn't participated in the interviews and Samuel Roscoe, a key supply chain expert due to his extensive knowledge about de centralized manufacturing and 3D printing. In the design section of the report (5.3.2), the designs are shown directly validated at the conceptual design section, meaning that this validation step is implicit.

2.2.3 Design Communication

After refining and optimizing the supply chain designs, the next step of the model is the design communication part where an **implementation plan** of the suggested design is established. This step is shown in the implementation strategy plan (chapter 6, implementation strategy plan).

2.3 Research sub questions

To achieve the design objectives, the proposed exploratory research sub questions are the following.

First of all, the main question to ask is the reason why drug 3D printing would be required in order to adapt the pharmaceutical supply chain to the new product requirements. What are the advantages that it offers or what production gap drug 3D printing fills?

SQ1: *Why would drug 3D printing be needed to produce personalized medicines?*

Secondly, after establishing why this new production method could be used for, it is essential to determine which requirements need to fulfil drug 3D printing to produce personalized medicine.

SQ2: *How can personalized medicines be achieved by 3D printing?*

Thirdly, it is essential to assess how the actual supply chain of the pharmaceutical companies look like. In order to answer this, it is necessary to research how the pharmaceutical companies are organized and structured. This leads to the research question:

***SQ3**: How is the existing supply chain of the pharmaceutical industry organized?*

Fourthly, it would be necessary to estimate how 3D printing could modify the existing supply chain. To be able to appraise this, first 3D printing of drugs will have been researched and then the implications and challenges of it will have been determined according to previous research questions. Then, the supply chain modifications are assessed. In order to do that, the two research questions required are:

***SQ4**: How can 3D printing affect the existing supply chain?*

***SQ5**: How can these effects be measured?*

2.4 Research Methods

This thesis is a **design-oriented study** that will deliver 4 different supply chain designs showing how the transport and logistics of pharmaceutical companies would be modified if 3D printing is adopted as a production method. As mentioned before, the design would require of a research part. This research step starts with the exploration of the challenges that surround 3D printing as a personalized medicine production method in order to come up with the requirements for the supply chain designs. The exploration consists in a literature review combined with semi structured interviews to experts from the supply chain itself, the pharmaceutical industry, regulatory experts from the medical field and from the 3D printing ground (Verschuren, Doorewaard, & Mellion 2010). These experts would come from the industry, supply chain or logistics managers in pharmaceutical companies and public research centres.

Interviewing has the advantage of adapting the questions depending on each subject's answer and his or her area of expertise. In addition, it is very useful at the exploratory stages of the research (Sekaran, 2006). And **literature review** includes all sorts of secondary data sources such as books, articles and internet sources like blogs and expert opinion sites.

Table 2 shows an overview of the research method and data sources used to answer each of the research sub questions. As mentioned, the research is based on a literature study complemented with semi structured interviews to field experts. The data sources are very broad due to the innovative character of the topic and its growing interest. As a primary source, the interviews and as secondary mainly: books, journals, articles, reports, case studies and blogs. Sub questions 1 to 3 were answered by the literature study, 4th and 5th with the interviews.

Table 2 Overview research approach. Source: this project

	Research sub question	Research Method	Data Source
1	*Why would drug 3D printing be needed for the production of personalized medicine?*	Literature review, interviews	Journals, books, reports, experts from the field (pharmaceutical industry and 3D printing experts)
2	*How can personalized medicines be achieved by 3D printing?*	Literature review, interviews	Journals, books, reports, experts of the field (pharmaceutical industry, 3D printing experts and regulatory experts)
3	*How is the existing supply chain of the pharmaceutical industry organized?*	Literature review	Journals, news, blogs, magazines, books, reports
4	*How can 3D printing affect the existing supply chain?*	Literature review, interviews	Journals, news, blogs, magazines, books, reports, experts of the field (pharmaceutical industry, 3D printing experts, supply chain and additive manufacturing experts)
5	*How can these effects be measured?*	Interviews	Supply chain experts and 3D printing researchers.

2.4.1 Literature review

The literature review provides a critical discussion of what have been published regarding 3D printing, drug 3D printing, personalized medicine and pharmaceutical supply chains. The aim is to show the reader that the author is aware of the state of the art regarding a specific topic (Gould, 2011). Many literature sources existed regarding drug 3D printing; however, due to the innovativeness of the topic, mostly were reports written by consultancies and pharmaceutical companies and websites. Nevertheless, few articles and books were also analysed.

2.4.2 Semi structured interviews

The purpose of carrying out semi structured interviews is to discover and build on the information that is important for the research and the interviewee knows it but the researcher may not have previously

thought about. In this way, the interview would be barely prepared beforehand, few ideas and questions to start from as well as a scheme that helps the researcher to conduct the interview (Gill, Stewart, Treasure, & Chadwick, 2008).

By using this qualitative research method, the aim is to get deeper understanding than the obtained by quantitative methods like questionnaires. **Semi structured interviews** are the best suited method to research about supply chain effects as little is known and deeper insight is required. This methodology is based on the interaction between interviewee and researcher (Clifford, French & Valentine, 2010; Gill et al., 2008).

Furthermore, it is necessary to have few questions or themes written down in order to have an interviewing line. These questions need to be designed in a way that promotes conversation and discussion. Also the researcher should be prepared to formulate questions during the interview (Clifford, French & Valentine, 2010). The interview questions were developed specifically for each of the interviewees depending on their area of expertise and adapted during the interview itself. From the literature review, few inconsistences and disagreements could be found regarding drug 3D printing manufacture from technical requirements to regulation and production techniques (section 4.3.6). Also, from the literature, few ideas about the supply chain effects of drug 3D printing were discovered and categorized to come up with the design requirements shown in section 5.3 (table 6). The first interviews were less structured and their findings helped to develop the questions for the following ones. All the interview questions divided by expert category and expert are provided as long as with their transcripts in appendix part B.

Interview procedure

Most of the interviews were carried out by phone due to the spread location of the interviewees; however, one was possible to carry out in person as a focus group (regulatory experts interview). The interview questions and transcripts are shown in the appendix part B. Each interview was recorded and notes were taken so afterwards, they were transcribed and analysed. Two experts asked to remain anonymous due to their collaboration with the industry or their own research, for this reason, in the following sub section of the actor classification some names substituted by X. The interviews ranged from 30 to 45 minutes, the prepared questions were asked and room was given for further discussion.

Actor classification

The interviewees were chosen depending on their background and expertise in the field of supply chain, pharmaceutical industry, 3D printing and personalized medicine. Their contacts were obtained from many online sources: articles, conferences, company's profile or public data mainly; but also from a social business related network called LinkedIn (I joined couple of discussion groups about 3D printing and 3D printing medicine were I was able to get contacts from experts and people from the field to interview). And also two direct sources: an in-house day at J&J at which I had the opportunity to attend and the Chief of this thesis committee, Professor Lory Tavasszy and Professor Bart van Hulst who gave me the contacts from researchers that they know.

In order to decide which group of experts to interview, the stakeholder's analysis (which is shown in the discussion section) plus the literature review results were combined. The aim of the interview process was the exploration of the main challenges and problems that either the literature pointed or that were contradicted or not clear. Some examples were technical requirements, regulation, limitations of drug 3D printing, concerns surrounding it and supply chain effects. For this reason, **experts that know about 3D printing and drug 3D printing** were necessary to get more insight regarding the topic. Apart from those, from the interest versus power grid (figure 44) it is seen that **pharmaceutical companies and regulatory agencies** are the ones with higher power and interest in drug 3D printing. For this reason, interviewing them would provide more insight into strategies to produce and commercialize drugs 3D printed at the same time of researching over regulation concerns. Finally, to answer the sub questions *How can 3D printing affect the existing supply chain?* And *How can these effects be measured?* Supply chain experts were required. Other actors with great interest and power are patients, hospitals and pharmacies; however, due to the innovativeness character of this technology, those actors couldn't provide the required knowledge. Their involvement in the research is left for future steps.

As table 3 shows, for this thesis 12 experts were interviewed; from those, 5 were related to 3D printing field, 3 were supply chain research experts, 1 expert that works in a pharmaceutical company and 3 regulatory experts.

Table 3. Classification of the interviewed experts. Source: this project.

Field	**Number of expert interviewed**
3D printing	3
Drug 3D printing	2
Supply chain experts	3
Pharmaceutical companies	1
Regulatory experts	3
TOTAL	**12**

In the transcripts of each interview the experts are separated according to the previous groups and their background is pointed. A summary of that information is shown in table 4.

Table 4. Table of experts organized in categories. Source: This project.

Field	**Expert**
3D printing	*Dr. Tobias D. Gantner* **Now**: HealthCare Futurists GmbH (incubator and innovation in healthcare catalyst) **Background**: Doctor and economist who has worked in patient care in major companies such as Siemens, Novartis and Bayer.
	Mr. Robert Palazzolo **Now**: Development engineer at Terumo cardiovascular systems **Background**: Master thesis on oral dosage forms by 3D printing in 1997.
	Dr. Pedro Costa **Now**: Postdoctoral researcher at Utrecht biofabrication facility.

	Background: Biologist specialized on the field of tissue engineering and the application of 3D printing tools in this field.
Drug 3D printing	*Dr. Erkan Aziziglu* **Now**: works at the Laboratory of Drug Delivery at Georgia institute of technology **Background**: Pharmacist (Bachelor and MSc.)
	Dr. Clive Roberts **Now**: Head of school Laboratory of Biophysics and Surface Analysis, Nottingham University. Current research on medicine development by 3D printing. **Background**: Pharmacist.
Supply chain experts	*Dr. Samuel Roscoe* **Now**: Lecturer and researcher on Operations Management at Sussex University. Teaches how 3D printing could affect pharma supply chain. **Background**: PhD in sustainable new product development. 14 years of industry experience in supply chain management and logistics.
	Dr. X **Now**: Professor in Additive Manufacturing Management, Nottingham University. **Background**: PhD on additive manufacturing and its economic implications.
	Mr. Sam Onukuri **Now:** Head/Fellow 3D printing & Netshape Technology Center in Cincinnati, Ohio. **Background:** Studied Biomedical engineering at Northern Illinois University.
Pharmaceutical company	*Dr. X* **Now**: High position at a global commercial level at TEVA Pharmaceuticals **Background**: Pharmacy. Worked in pharmaceutical leading companies: TEVA, GSK and AstraZeneca.
Regulatory experts	*Mr. Jaap Koster* **Now**: Director of the Pharmaceutical consultancy service (PCS) **Background**: worked in and for pharmaceutical and biotech companies.
	Dr. Hans J.L. Meerburg **Now**: Grondmeer Farma B.V **Background**: Pharmacist
	Dr. R.H.L.M (René Maassen) **Now**: Maassen Pharma Consultancy **Background**: Pharmacist who worked for the Dutch Health Ministry

As conclusions from this analysis, all the interviews were carried out successfully and all the interviewees were experts of the pharmaceutical, supply chain or 3D printing field accordingly. Their proficiency was due to their studies (university or PhD researches) or due to experience. Nevertheless, their expertise in their field was unquestionable; so from all the interviews the results are the most valid opinions that could be obtained from leading experts in their field of expertise.

Interview analysis

The analysis was based on Burnard (1991) method due to the nature of the interviews (as mentioned, all of them were semi-structured and open-ended interviews). The method was a bit simplified from Burnard (1991) but it consisted in the main points: making notes and categorizing the data (exploration phase), reading carefully the data again, generate categories to organize the data and collapse them to form more general ones (specification phase). After that, produce a list of headings, make adjustments to the categories, organize the items of each code together by finding the core categories (reduction) and finally, link the data with the literature (integration). The main findings are presented in chapter 5 but all the procedure described to get to those key words is presented in the Appendix Part B under Interview analysis title.

During the interviews, data analysis was started in order to continuously check which terms were the key points for drug 3D printing and which information was missing or the interviewees were not agreeing upon.

The final step was to check the interview data's **validity** to reduce subjectivity and bias**.** According to the method, the way to check that was a *member checking approach* which consists in checking the categories, interpretations and conclusions made by the interviewer with the members from whom the data was initially gathered. In order to do so, the interview transcripts with the key words highlighted and the data categorization were sent back to the interviewees. After receiving the researchers' comments, few adjustments were done to the previous findings. Furthermore, a last interview was carried out to Dr. Sam Onukuri and the conclusions from the data analysis were checked for consistency.

2.5 Research and Design relevance

As previously pointed, drug 3D printing is a current researched topic that raises interests in all imaginable fields, not just regarding innovation or production technique; it reaches all aspects from logistics to financial interests. Nevertheless, my research is focused on the **effects that this new production method would have on the supply chain of pharmaceutical companies.** The main reason for that is the missing link between drug 3D printing and the consequences that it would have on the logistics and transportation. Few ideas and recommendations are pointed in newly published articles and other internet sources but any deeper analysis on this does exist.

Also, the effects of 3D printing go beyond the companies themselves, there are more stakeholders involved: customers and suppliers, policy makers and the other industries that depend on the medical industry like collaborators or partners. The nature of the problem includes societal relevance and scientific contribution. First, the **societal relevance** of it involves understanding the implications of changing the drug production system in the whole society in order to know how to act accordingly. From the governmental point of view, changing the manufacturing model needs new policies and regulations to ensure quality, responsibility and traceability of the products; from the citizens, this will provide knowledge about medication and how these trends would improve their health and quality treatments. Lastly, for the companies, this research would provide insight of how to predict innovations' effects. Secondly, the **scientific relevance** of it involves finding the technology state of drug 3D printing and the key challenges or breakthroughs needed to enter the mass market.

Furthermore, moving backwards to a more general picture, the pharmaceutical field is a key pillar in the world where we live today. Its actors and effects go beyond what is thought. So, the modifications that it could experience are of primordial relevance and deserves our attention.

The deliveries of this master thesis are 4 supply chain re-designs where 3D printing is considered as a production method for personalized medications in the near future. The alternatives are complemented with strategic recommendations for product and supply chain managers of pharmaceutical companies to assess them in their current and short term future decisions.

2.6 Research and Design scope

The focus of this study is on determining the implications that drug 3D printing would have on the transport and logistics of the pharmaceutical companies. However, the study is limited to:

- **Geographical scope:** Western Countries

The geographical scope is not because of lack of data, is because the strategies and supply chain that pharmaceutical companies use in the western countries (mainly EU, the US and Japan) differ from the ones used in developing countries (further reflection on the scope is provided in section 7.5). Although building a case for drug 3D printing in the developing countries is of great interest, it is also of great relevance researching the effects on a well stablished but still inefficient western supply chain.

- **Time horizon:** next 10-15 years

Technology continuously changes, new tools appear and other disappear at the same time. Giving recommendations and assessing a technology today cannot be done in a very long time horizon. And it is even more complicated with drug 3D printing given its current adoption phase. The time horizon is the one suggested by the experts during the interviews.

- **Supply chain:** make and delivery

The supply chain effects analysis would be limited to manufacturing and delivery stages mainly because most of the data gathered from interviews and literature points to these stages as the most affected.

2.7 Research and Design framework

To provide a clearer understanding of how the research and the design approaches are interlinked, figure 7 depictures each step of this study linked with the chapter that belongs to and the research questions and objectives answered.

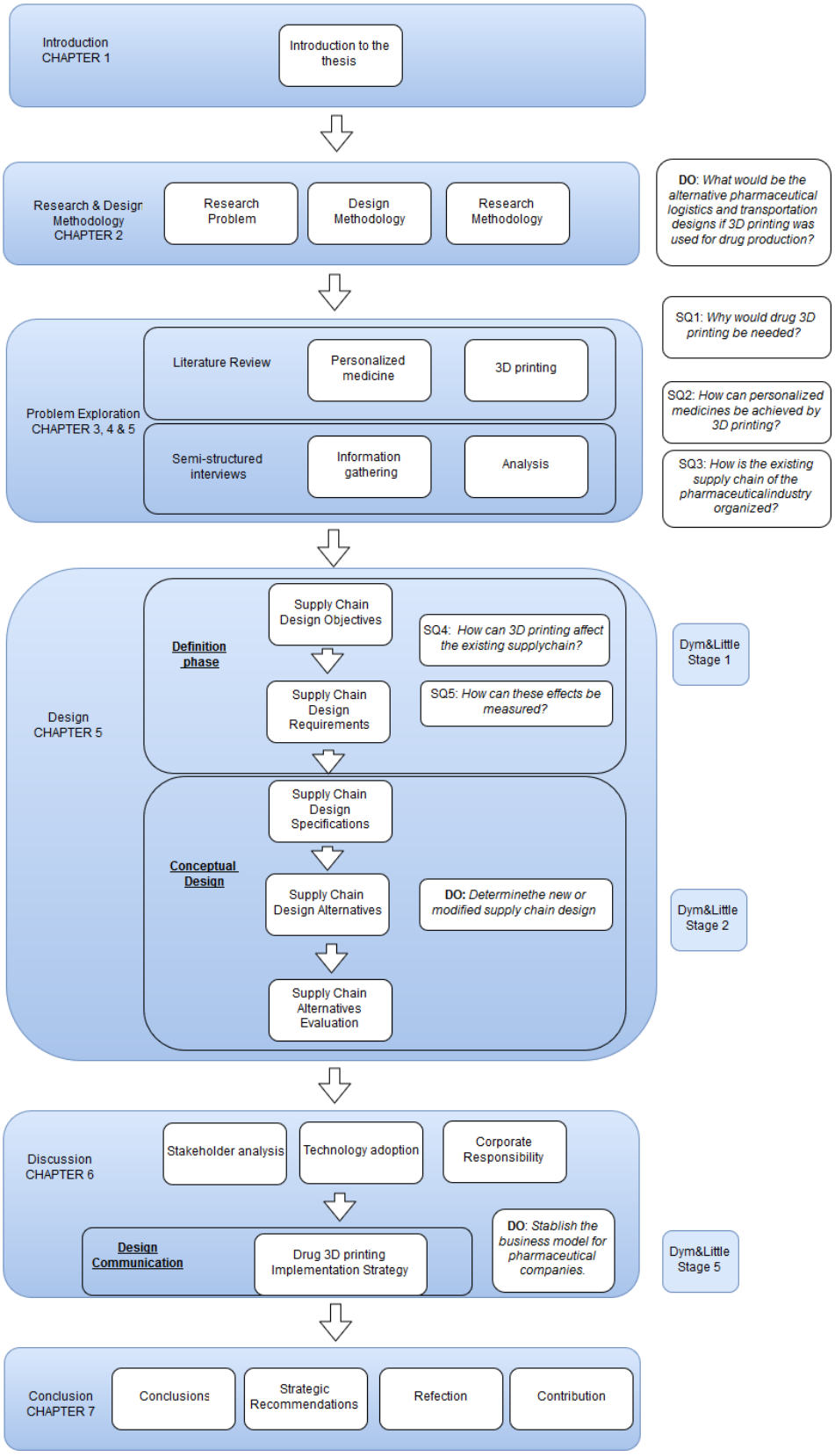

Figure 7 Research approach scheme. Source: this project

The first chapter includes the introduction to the thesis; the second chapter explains the research problem and design objectives. From the design objectives, the research sub questions to be answered are established and provides a detailed methodology of how to do so. Problem exploration includes chapter 3 and 4 and first part of chapter 5 which will provide the main requirements and challenges to implement personalized drug 3D printing. Chapter 3 and 4 contain the literature review on personalized medicine and 3D printing. Also, first part of chapter 5 delivers the interview information gathering and analysis (problem definition phase of the 3 stage design model). In the second half of chapter 5, the objectives are transformed into supply chain requirements to design the 4 supply chain alternatives (conceptual design stage of the 3 stage prescriptive model). Then, the design specifications determine how the designs will be depictured, and after doing so, they are evaluated in order to assess their weaknesses and strengths (also in the conceptual design phase of the 3 stage prescriptive model). Chapter 6 discusses the challenges that drug 3D printing faces in terms of technology adoption rate and with the stakeholder's analysis and corporate responsibility in order to build an implementation strategy plan for drug 3D printing (design communication stage of the 3 stage prescriptive model). To sum up, in the conclusions section (chapter 7) the supply chain designs are linked with the implementation strategy and strategies to product and supply chain managers. The aim is to help them make the decisions of how to include 3D printing as a production method and how the pharmaceutical supply chain will be affected. Furthermore, it is also included in this last chapter the research contribution (what does this thesis offer to managers and academics) and the academic reflection (generalizability of the results, uniqueness of the pharmaceutical field, etc.).

CHAPTER 3. PERSONALIZED MEDICINE

This chapter corresponds to one of the three chapters that form the problem exploration part of the research. In the scheme of figure 8 the position of this part of the report is clarified. A more extended version of this figure was already shown in the previous chapter (figure 7).

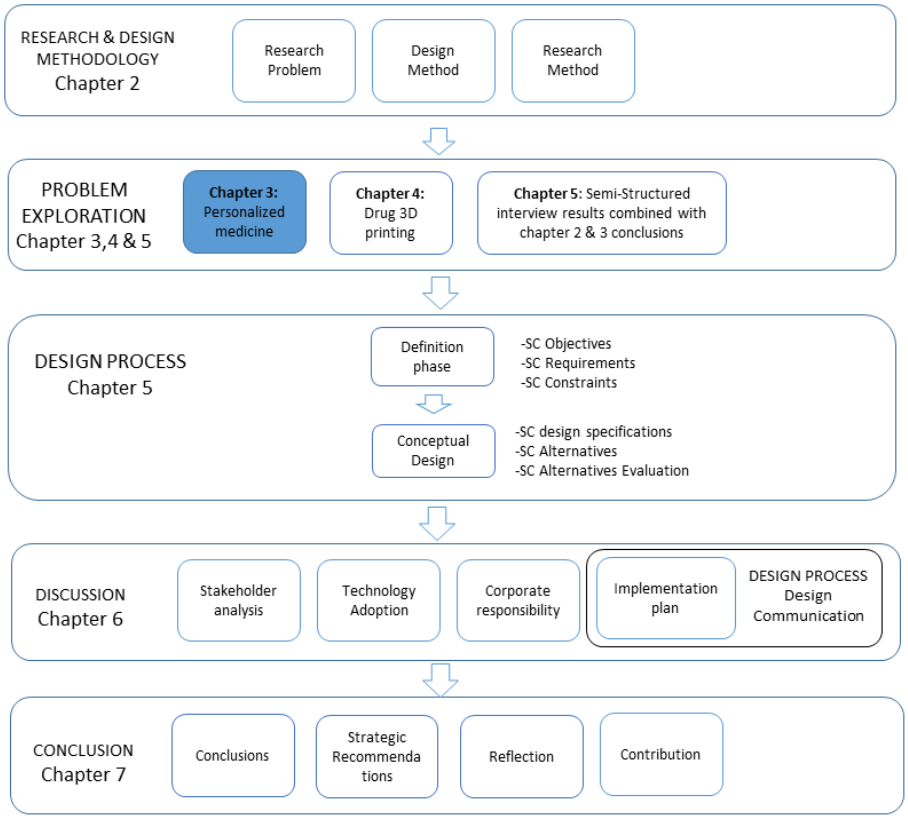

Figure 8 Position of Chapter 3 in the whole research framework. Source: this project

3.1.Introduction

Since the completion of the first draft of the Human Genome Project 10 years ago, the field of genomics (the study of genomes) has evolved extremely fast until a point that now technologies do exist by which it's possible to analyse and interpret genetic data in an efficiently and cost effectively way (Chan & Ginsburg, 2011). Personalized medicine has long been considered as the next big game changer in healthcare. In 1998 the first drug adapted to a specific patient spectrum was launched by Genentech. The drug is called Herceptin, which is a treatment for breast cancer patients with a specific receptor. However, despite its success, personalized medicine is still after near a decade, not largely distributed (Padilla & Kulkarni, 2014). Nevertheless, before studying the challenges and opportunities that this new type of medicine is facing, first a more detail research about this topic will be provided.

Current medicines are designed for the "average patient" and because of this lack of specialization, they are not as effective as they could be and some others are even poisoning them. Not producing the medicines taking into account each patient's needs is a problem of extreme importance worldwide. It can be pictured by statistics: just considering the top 10 most consumed drugs in the US, between 1 in 25

patients and 1 in 4 patients that take them are actually helped by the medication (see figure 9). However, the situation is even worse, because some drugs are harmful to the patients that take them due to genetic differences. A clear example of this was Merck's experience with rofecoxib (Vioxx®). Not far from its approval by FDA, Rofecoxib became a $2.5 billion per year blockbuster. However, it had to be withdrawn from the market by September 2004 due to the evidence that showed how this drug increased the possibilities of suffering a heart attack. Rofecoxib example clearly illustrates the crucial need to identify patients in late phase clinical trials that might be at risk for serious rare adverse effects. Safety concerns are driving many different innovations in the diagnostics industry and most likely will contribute to the evolution of personalized medicine (Lesko, 2007; Schork, 2015).

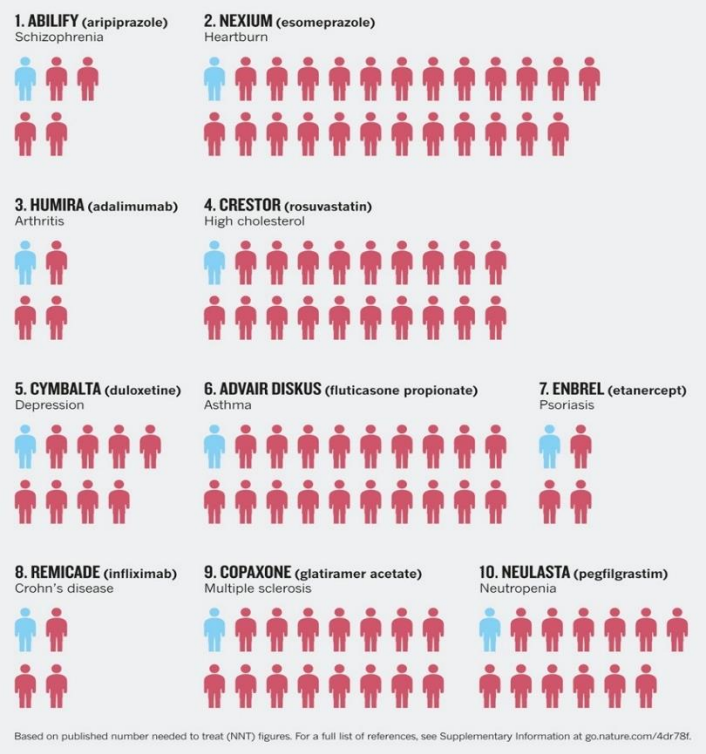

Figure 9 Imprecision of medicine. Source: (Schork, 2015)

Personalized medicine consists in a way of delivering targeted medicines safely and effectively to each patient. However, this new approach needs a change in the current manufacturing processes, clinical trials and in the research and development stages (Jonathan, & Karim, 2016).

In order to change the current paradigm, the roots of the drug production need to be changed. First of all, provide diagnostic tests to link a person's genome with the required medicine and then produce the medicines linked with the genotype that they are useful to treat. This would change the existing clinical trials into N-of-1 trials (studies that concentrates upon a single person). The basis of these trials defend that collecting sufficiently information during a long time, the response or non-response to a treatment is established. Sometimes N-of-1 trials would not be feasible or appropriate, for example when the effects of a drug or a chemical compound has to be established on the whole population. Nevertheless, in cases such as the one of concern, like testing drugs for rare diseases or experimental drugs for people who do

not respond to the established treatments, the use of N-of-1 trials has resulted very useful. Furthermore, studies researching the safety and dosages of a new drug could be determined by these tests (Schork, 2015).

In a recent report, Paving the Way for Personalized Medicine, FDA's Role in a New Era of Medical Product Development, FDA states that tailored medicine is thought of as the **adaptation of medical treatment to patient's needs, characteristics and preferences during all stages of care, from prevention, diagnosis and treatment**(FDA,2013). In order to create personalized medicine, differences in people's genes, environments, lifestyle and gender need to be taken into account. The usage of genetic information will be utilized to guide medical decision making to make tailored treatment decisions and risk predictions and provide personalized drug treatments (Ginsburg, & Willard, 2009). Moving from a "one-fit-all approach" strategy towards personalized drugs offers a step forward in healthcare (FDA, 2015; Hamburg & Collins, 2010).

When you think about personalized drugs the first that comes to your mind are very complex medicines that target a specific gene. The top area that has been researched until now is oncology due to its specific relationship between gene and disease. However, more illnesses are obtaining attention: immune-related diseases, transplants, infectious diseases and cardiovascular. The key terms to evaluate the feasibility of development of personalized drugs are: understanding the basis of disease differences, the clinical relevance of markers of disease heterogeneity, the technical tractability and feasibility of measuring markers and the relative economics of the personalized drugs (FDA, 2015).

The main objective for personalized medicine is **having precise and reliable diagnostic tests that identify patients who can benefit from special therapies**. A part from that, patients have to trust diagnostic tests (Hamburg & Collins, 2010). Complications must be overcome to achieve these objectives. These include scientific challenges, like determining which genetic markers have the most significance, steering clinical studies to determine genetic variations that are correlated with a medication response and limiting the off-target effects of gene-based therapies. There are also policy challenges too, for example finding a level of guidelines for genetic tests that protects patients and boosts innovation at the same time (Hamburg & Collins, 2010).

However, the need for customized medicine goes further than just satisfying customers' needs, it also solves a pharmaceutical problem: "the productivity issue". This refers to the fact that although pharmaceutical R&D has increased twice over the past decade, there has not been a corresponding increase in commercial new chemical entities. The reasons for this "crises" are controversial. However, one of the main reasons of it is the exhaustion of the blockbuster model. In the past, the blockbuster model of drug development has produced molecules that have had an immense impact on improving several serious public health-care problems. Large Pharmaceutical companies' strategy have continued with the main focus on this model, even as though many pharmaceutical leaders have expressed serious alarm about the increasing costs of producing a successful new molecular entity (the development costs range from $750 million to $1.5 billion) and the lengthy developing time that it needs (approximately around 8 to 12 years). Usually the success of the blockbuster business model is attributed to the fact that blockbusters' profits more than compensate for the numerous molecules that don't pass the initial phases

of clinical testing. However, the usage of molecular biomarkers have the potential to improve productivity and enrich clinical trials with molecules without adverse effects and to individualize dosing to each patients' needs (Rusu, et al., 2011; Lesko, 2007).

There are substantial barriers to make N-of-1 trials and personalized medicine worldwide. The main barrier are the interests behind actual clinical trials and current medicine production methods. The entities with stronger interests and power regarding this matter are regulatory agencies, physicians, researchers and pharmaceutical companies. First of all, producing treatments used by millions of people is less costly and with greater benefits. And secondly, tailoring medicine is costly. For instance, just for sequencing the affected cells with a growing tumour to know which tumour does the patient suffers from, it costs between $5000-7000. Nevertheless, ultimately political parties and regulatory agencies will end up supporting N-of-1 trials and personalized medicine as they would save millions of dollars used to cure diseases for which they are not suitable or inappropriate interventions (Schork, 2015).

To sum up, personalized medicine is a worldwide need that with some incentives could be achieved. It is already becoming a reality since many pharmaceutical companies are moving towards this new type of medicine as it will be explained in the further sub sections.

3.2 Main goals of personalized medicine

Personalized medicine thrives for:

- Treatment of diseases that until now were incurable.
- Better life quality (less side effects and better targeted treatments)
- Less invasive surgeries (personalized treatment also include new techniques such as liquid biopsy that avoids surgical intervention to detect cancer)
- Reduce healthcare costs.

All in all, personalized medicine helps patients to live longer and have a better life (What is Roche Personalised Healthcare all about?, n.d.; Davis, Ma, & Sutaria, 2010).

3.3 Drugs to be personalized

Rare diseases, infectious diseases (VIH, Hepatitis B and C**), cancer** (melanoma, thyroid, endometrial, colorectal, breast, stomach, lung)**,** diseases affecting the **Central Nervous System** (Alzheimer and Huntington), **cardiovascular diseases, diabetes, arthritis, depression**, **inflammatory diseases**, **immune-mediated inflammatory musculoskeletal disorder**, etc. Complex diseases, complex referring to its molecular pathway and involving many genes will be the ones personalized in the upcoming years. Also they are called complex because the past efforts to cure them have been non effective and imprecise (The benefits of personalized medicine, n.d.; Consumer health, n.d.).

3.4 Infrastructure required

The infrastructure required to perform diagnostic tests for personalized medicine is more complex than the existing one. But not only for diagnosis, drug discovery and development would need to adapt to adopt personalized medicine (Ginsburg, & McCarthy, 2001). One example to illustrate the need to adapt the existing infrastructure is the usage of diagnostic tests for many diseases caused by viruses and bacteria

like genital herpes disease. Specifically, this disease has available a rapid and specific test to detect the virus in blood or serum. However, as a recent survey indicated, it is underutilized because 82% of the doctors weren't aware of it. Thus, education and new systems of sharing information are needed to teach physicians and patients in order to exploit all the information that these tests offer. Furthermore, doctors need an infrastructure with which they can access to complete patient medical records such as medical history, staff notes, allergies and interactions, drug prescription history and all laboratory test results. To provide personalized medicine, a complete integrated medical record system is needed so physicians could access all their patients' relevant information in real time (Lesko, 2007).

Regarding drug discovery and development, it has by tradition been a linear process with little feedback from later stages (figure 10). The approval of personalized medicine as a drug development strategy, will necessitate an integrated 'knowledge management system' because the data needed for the drug design will be captured at various phases of development (figure 11). Research feedback from later development stages will be applied to early phases of drug discovery such as selection and validation of targets and small molecule screening; so an integrated 'knowledge management system' will be used. This system will facilitate rational drug design around molecular diseases (Ginsburg, & McCarthy, 2001).

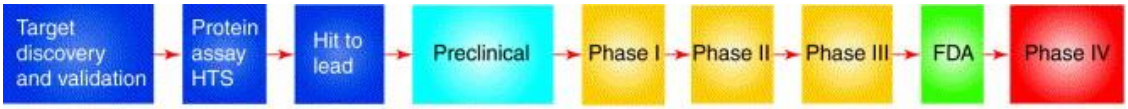

Figure 10 Drug R&D process how it is currently organized. Source: (Ginsburg, & McCarthy, 2001)

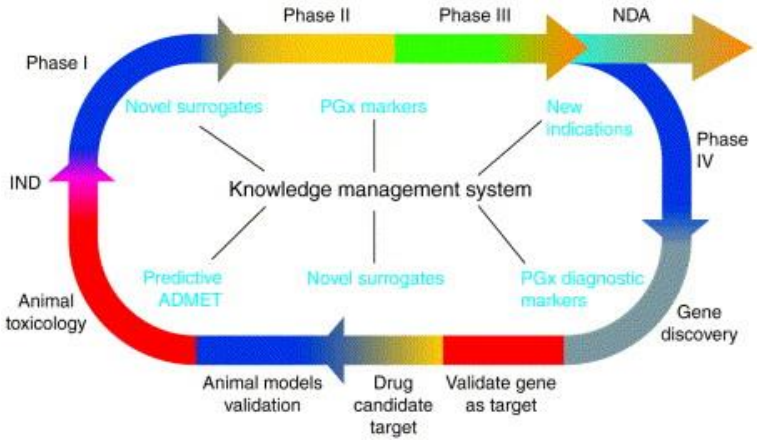

Figure 11 Drug R&D process how is envisioned to produce personalized medicine. Source: (Ginsburg, & McCarthy, 2001)

Markers predicting pharmacodynamics and pharmacogenomics of drug toxicity in humans should be introduced into all 3 development phases where patient stratification and selection can be guided regarding the markers to ensure safety and efficacy. Furthermore, careful monitoring during clinical phases will lead to pharmacogenomic markers that will be further used to select the patients to whom the drug will be administered but also to apply this information to earlier stages of R&D of new drugs. Besides, molecular profiles of those patients that are most likely classified as non-responders in early phase I and II of clinical studies represent a great chance for pharmaceutical companies to start new lines of research and find novel therapies (Ginsburg, & McCarthy, 2001).

A **diagnosis section** which includes more information about biomarkers and how to customize patient's treatment is included in Appendix Part A under the title of personalized medicine.

3.5 Opportunities and challenges

Personalized medicine is projected to create value for the patient and the healthcare system but exactly how will be the value distributed?

From the **patient's perspective**, the value increase refers to a more accurate diagnosis; however, the number of nonresponses in some genomic tests is greater than fifty percent. That means, that more research and improvement of those tests is required. However, even with this low accuracy, diagnosis tests will reduce the drug waste on non-responders. From the **pharmaceutical point of view**, some high-value drugs will decrease in market share, whereas other drugs will capture value by higher prices and longer duration of the treatment even though they will be just for a population segment. In the case of **diagnostic companies**, they will capture value through customized diagnostic tests (Ginsburg, & McCarthy, 2001). A part from value, what are the opportunities that personalized drugs offer and the challenges that need to be overcome to become a reality?

Opportunities

The productivity of pharmaceutical companies has lowered during the past years as they have relied on blockbusters and easy targets that are getting more and more difficult to find; thus, their research capacity to discover new products is jeopardized. PMx has the possibility to be the breakthrough that pharmaceutical companies need to solve this situation (Padilla & Kulkarni, 2012). By adopting PMx, pharmaceutical companies are embracing a new business model in which patients are segmented according to their genomic needs. Also, the medical decisions and practices are tailored to reduced set of individuals. At first sight, this reduced number of customers will lead to a minor revenue stream, but the profits will be higher. In fact, developing PMx will reduce the costs of research and development of compounds and an increase in manufacturing and distribution efficiency. Furthermore, the timeline that depictures from R&D until launching the drug into the market will be reduced due to clinical trials' time (Ginsburg, & McCarthy, 2001; Padilla & Kulkarni, 2012).

Besides the obvious social benefit of treating patients according to their needs, pharmaceutical companies can charge more for these targeted therapies and the clinical trials required participants and time are reduced as they are targeted to a much smaller patient population. For example, Pfizer's Xalkori just treats approximately 5% of lung cancer patients. Moreover, PMx speeds up the development of meds and increases pharmaceutical productivity. The clearest example is Zelboraf, a melanoma drug developed by Roche which was the fastest-through-the-pipeline recently (Staton, 2014).

The opportunities that personalized medicine offers to patients and physicians is the possibility to provide the right drug and the right dose, to the right patient, at the right time. Thus, the added value that customizing medicine has is a **high probability of a drug's desired outcome**, **low probability of side effects**, **reduced costs** and targeted therapies and **preventive strategies** instead of just reactive medicine. To sum up, a better health and healthcare overall (Ginsburg, & McCarthy, 2001; Pennic, 2014).

An example that explains the previous commented is the case of anti-HIV drug personalization. Physicians have improved significantly the success rate, governments have maximized the therapy value and the patients' life has been prolonged. Because of the new personalized therapies, HIV has moved from being a deadly disease to a chronic and manageable one with efficient and affordable treatment. Also pharmaceutical companies have capitalized upon these benefits, after the success of HIV treatment, Gilead Sciences Inc. has become the world's second-largest biotech company, after Amgen Inc. (Padilla & Kulkarni, 2012).

Requirements

Despite the impact that genomic testing could have on healthcare and the positive opinions expressed by many researchers and physicists, many challenges must be overcome to enable their integration into the daily practice. Its failure so far can be attributed to 5 main requirements:

- **Regulation**
    - **Regulatory standards**: in order to enhance innovation but ensuring patients' safety, an option would be to have an approval system in which diagnostic tests and drugs could be released after completing partially the clinical trials under a label such as 'under study'. Patients' first-hand experiences will be part of the clinical trials and will adjust clinical claims. This small change in the actual regulation system will allow medicine and diagnostic tests developers to enter the market rapidly and assess their effectiveness (Ginsburg, & Willard, 2009; Padilla & Kulkarni, 2014).
- **New business model and costs** (mentioned in the opportunities sub section)**.**
    - Pricing, billing and reimbursement system
- **Funding (**the development of PM requires funding either privately or publicly**)**
- **Research**
    - **PMx required equipment:** biometric devices and personal imagers or scanners are required if personalized medicine becomes a reality. These patient devices can be combined with biomarkers. Those include for example heart rate body surface measurements for people with chronic heart diseases. Companies such as Apple and Google are already producing hear-rate sensors and body monitors (Padilla & Kulkarni, 2014).
    - **New trial design to test biomarkers.** The critical decisions regarding trial design are defining target population, the biomarker's read-out and in which type of trial include biomarkers: supporting or registration (Cattell, Chilukuri, & Levy, 2013).
- **Education**
    - **Medical education:** knowledge about the existing tests and how to implement them (Cattell, Chilukuri, & Levy, 2013).
- **Professional capabilities**
    - Adequate **sample collection and data analysis**: sample collection and storage is essential to perform diagnosis tests; the correct sample and of the required quality are necessary to obtain reliable test results (Cattell, Chilukuri, & Levy, 2013).

- **PMx capabilities:** many pharmaceutical companies believe that the capabilities required to adjust to personalized medicine are far beyond the existing and that results in a huge investment. However, in reality, the incremental cost of developing new capabilities over the existing company's costs could be absorbed within the existing research and development budget.

Most importantly, the drug developer must be able to achieve the requisite return on investment despite the restricted market size. In addition, drug development costs may be increased due to the complexities of biomarker analysis and diagnostic development. Molecular profiling is an emerging science, and several large and expensive drug development programs have faltered due to the selection of the wrong biomarker to guide patient selection. Trials involving **biomarkers** are attracting high interest from researchers, but require new competencies in trial design, data analysis and investigator expertise in sample collection and management (Ayers, 2010).

In order to find genetic biomarkers that allow the prediction of complex diseases, apart from the 5 previous requirements, large and well characterized patient populations, a deep and detailed understanding of disease pathways in the human body and also, computer based methodologies which can analyse quickly and effectively massive amounts of gene and protein data. But not only that, systems that are able to integrate all the data from genetics and molecular profiling with traditional clinical data and provide an understandable profile that accompanies each patient are required (Ayers, 2010). Furthermore, providing education to physicians and patients is essential to implement this innovative type of medicine. Governments need to be involved and play and active role in solving public's concerns and drafting legislation to protect patients from being discriminated by insurance companies and healthcare employers. At the same time of promoting educational practices addressed to physicians and patients (Ginsburg, & Willard, 2009).

Nowadays, patients can consult uncountable websites and online forums to get more knowledge about their diseases. The problem is that the information quality ranges from helpful and accurate to completely fallacious. Personalized medicine will transform how individuals learn about their health providing them with more direct and accurate information regarding their therapy and post-treatment as well (Padilla & Kulkarni, 2012).

Regulatory environment

The FDA has recognized personalized medicine as an effective solution towards a sustainable drug development model. A proof of their commitment is seen in the growing number of pharmaceutical products approved by the FDA that are accompanied with genetic tests for prescription or dosage. By 2009, the number of products that recommended a genetic test were up to 200; but the number hasn't stopped growing until now (Table of Pharmacogenomic Biomarkers in Drug Labelling, 2015).

Depending on the intended use of the diagnostic tests, different regulation is applied. Diagnostic tests are divided into four groups: those tests that need a 510(k) pre-market submission, approval via PMA (pre-market authorization), de novo reclassification or those considered as "Home Brew" or in-house assay. 510(k) pre-market submission is for those tests that are shown to be equivalent to a tests that does

already exist in the market. PMA regulation is needed for new diagnostic technology that's not equivalent to an existing one. De novo reclassification is necessary for those devices with low to moderate risk that cannot be compared to any existing device. Normally FDA asks for this regulation after a 510(k) is filed and no comparable devices are found. And finally, "home brew" tests are prepared in an established laboratory for a patient sample sent to the lab from a doctor's Clinique and do not need any special regulation to commercialize them but at least, the required documentation that classifies the test into this category (Liotta & Petricoin, 2011). Diagnostic tests for personalized medicine can opt for various of the paths suggested above. Roche, for example, adopted PMA path for its BRAF test that accompanied its drug Zelboraf, whereas Pfizer adopted 510 (k) strategy with its ALK test. The trade-off is between the time required to develop the diagnosis test and the control over the test quality (McKinsey&Co, 2013).

The requirements that the testing device needs to fulfil are designed to **ensure the effectiveness and safety of the product** for that specific intended usage. A suggested way to encourage personalized medicine is to simplify the regulations' path for these innovative technologies and then a stricter control of the accepted diagnostics. Although there is a general agreement regarding a change in regulation to encourage personalized medicine, it is not crystal clear how to achieve it (McKinsey&Co, 2013).

Reimbursement

A part from the diagnostic test regulations required to commercialize any diagnostic test, another important factor for the advance in personalized medicine is the cost of these tests and treatments. More than the costs themselves, what matters is who is going to pay for them? Are private insurance companies or public health systems going to reimburse these costs to the patients? Reimbursing the cost of these tests will enable the spread usage of personalized medicine and it will provide evidence of the benefits and cost savings that customized medicine has over the current reactive type of medicine. However, insurers encounter the problem of high membership turnover and subsequently they cannot retrieve the long-term cost benefits of the already reimbursed genetic tests. The actual policy regarding reimbursement of genetic tests establishes that only will be covered those screening tests which are performed because a clear link between symptoms or personal historic records of disease and the current patient's state does exist. Also, the reimbursement policy covers those tests that are explicitly authorized although they do not fulfil the previous requirements. Such a policy needs to be updated to enable the predictive side of personalized medicine (Deloitte Center for Health Solutions, 2009).

Personalized medicine is a health care priority for the governments of US and Europe. In the case of the US, many laws supporting genomic and personalized medicine have been approved. For example, the Genetic information non-discrimination act which ensures privacy of personal data against misuse in employment and health insurance; the Genomics and Personalized Act which pushes the development of personalized medicine to improve the quality of health care; and HSS Personalized Health Care initiative which is designed to enhance safety and health care quality for every American patient. Regarding reimbursement, the US government has approved a law called the American Association of Health Plans which encourages genetic testing for preventive care (Ginsburg & Willard, 2009).

Reimbursement determines the penetration that molecular diagnostics experience. For example, in France the penetration of those tests is higher than when compared to the UK or Italy where the coverage is lower. This landscape hinders innovation and a reform is needed to boost personalized medicine innovation and usage (McKinsey&Co, 2013).

Also it's true that reimbursement is not necessary for early adopters of diagnostic tests. Since the early diagnostic tests, many patients have paid for these treatments from their own pockets. The costs of a single of these tests is around $3,000. The willingness to know of some patients is stand upon the price in some cases. The same happen with vaccines, for example, VPH vaccine was paid in its early commercialization in Spain. Regardless its price (from 360 to 450 euros), many women purchased the vaccine due to its probable positive health effects (La vacuna contra el cáncer de cuello de útero, gratis en España desde septiembre, 2016; La vacuna del virus del papiloma humano podría erradicar el cáncer de útero en 30 años, 2008). Nevertheless, there are some cases in which Medicare and private health insurance companies did not reimburse the costs of the tests in the beginning but after some time they accept. For example, the case in 1006 of BRACAnalysis for breast and ovarian cancer diagnosis (Padilla & Kulkarni, 2012).

Physicians are now reimbursed according to how many drugs they administer, but not on the amount of time they spend with the patient to get an accurate diagnosis. A change in paradigm is necessary. In the US there's a new version of health insurance called "concierge medicine" or "direct care" which consists in getting doctor's advice 24h by phone per 7 days a week plus one annual complete physical exam by approximately between $59 and $137 a month. This practice model is growing recently as it is attractive bidirectional: patients get more personal care and physicians have less pressure as they have less patients and can spend more time with them. This new medical practice has many benefits but also drawbacks that have to be balanced: not all patients can afford it, more physicians are required, etc. A part from paying for specific diagnostic tests, people are willing to pay for personalized healthcare too. (Padilla & Kulkarni, 2012; Gunderman, 2014). This is practiced by doctors who step outside the traditional health insurance system. In most cases, they give service to their clients by phone or email and if their patients need to go to the emergency room, they are likely to meet them there.

3.6 Companies' position

Although its promising perspective, personalized medicine hasn't had the expected impact. However, the industry is now willing to change the current paradigm thanks to recent advances in the field of diagnostic technologies and in disease understanding. In order to capture the market value that personalized medicine offers, some companies have incorporated this new business model into their corporate mission while others have adopted a wait-and-see strategy. Market leaders such as **Roche, Novartis, Lilly** and **Pfizer** have already entered the list of early adopters of personalized medicine. Instead of building the required infrastructure in-house, several leading companies are buying out smaller genomics companies. This is the case for example of Novartis who acquired Genoptix in 2011 or **GlaxoSmithKline** who acquired Human Genome Sciences the year after. Both acquired companies were some of the earliest in using genetic information to develop new drugs. A part from those pharmaceutical giants, small start-ups are

getting interested in customized version of medicine and personal genomics. Some examples of them are **Prometheus labs, Genomic Health, XDx, deCODE Genetics** and **DNA Direct** (McKinsey&Co, 2013).

Roche is currently the market leader in personalized medicine with an approach to breast cancer with their therapies targeting HER2 gene. Although the number of approved drugs which require a diagnostic test for a particular biomarker that are already in the market were just 7 by the end of 2014, there are many waiting in the pipeline to be approved. The US market for predictive personalized drugs will double, increasing from $9,2 billion in 2013 to $18,2 billion in 2019. Today, personalized treatments are being offered for metastatic melanoma (BRAF-positive), metastatic breast cancer (between 15-20% of the patients are HER2 positive), non-small cell lung cancer (between 10-30% of the patients are EGFR-positive and more than 8% are ALK positive), viral infections such as Hepatitis B, Hepatitis C and HIV and stomach cancer (16-22% of the patients are HER2 positive) (What is Roche Personalised Healthcare all about?, n.d.).

Other pharmaceutical companies that are disrupting the market, but far from Roche's leading position, are **J&J** (with their Janssen unit specialized in personalized medicine) and Novartis. In the next group which are called "breakways" are included **AstraZeneca, Bristol-Myers Squibb** and Pfizer which are fast followers to this disruptor field. The last group of followers are **Sanofi, Amgen** and **Merck** which are developing their capabilities to embrace the field of personalized medicine but are not ready yet to do so. The laggard in this field of PMx is **Boehringer Ingelheim** who is now starting to invest in PMx (Staton, 2014; Big Data Meets Personalized Medicine, 2014).

Also, **Teva pharmaceuticals** has a strong focus on personalized medicine. The personalized products that TEVA is currently working on are divided into these main areas: multiple sclerosis, Parkinson's disease, NTEs, Respiratory, Huntington Disease, Pain and immunology. Moreover, they use omics and big data to reposition existing drugs, to look for other applications that the current drugs could have. The questions that the use to define these research units are: are there PK and PD markers that we can develop that help us to design their clinical trials in a more efficient and effective way?, are there any paths that we haven't characterized?, are there any problems with the existing drugs, do we understand the toxicology paths?, can we develop companion diagnostics? And can we reposition marketed drugs? Their aim with personalized treatment is to predict with greater precision the efficacy and safety of treatments (Teva Pharmaceutical industries Ltd., 2015).

A part from few companies that are pursuing PMx by investing all their existing capabilities, most big drug companies will take the approach to combine the commercialization and development of both "one-size-fits-all" products and customized drugs (Ferrara, 2007).

Company's required capabilities

If a company wants to develop itself in the field of personalized medicine, a part from having the right tools and processes, a combination of technologies, skills, knowledge and organizational processes need to have been developed over time. These **organizational capabilities** need to be **cross-functional**, so shared between departments and not in isolation. For example, in order to develop a new product in oncology for example, experts from different departments need to be put together. These include genetic research professionals, finance, marketing and sales and also have the management team involved. The

research professionals are needed for the biomarker research and development, finance experts for establishing the price and the economic models and the marketing and sales people for bringing the product to the market. All the departments need to work in collaboration in order to bring value to every part of the value chain from the early discovery through the development to commercialization and life-cycle management (Padilla & Kulkarni, 2012).

Companies are already getting used to cross-collaboration, but more in depth changes in the company's way of working need to be made to allow the development of personalized medicine. Some initiatives are the following:

- Encourage the understanding that **drug customization is a necessity** to fill pharmaceutical pipelines with new candidates and gain strategic commitment from all company's departments. The overall R&D strategy and portfolio planning need to be aligned around personalized medicine in order to be effective. Although the need for this alignment is quite obvious, many times the employers in charge of biomarker research and customized drugs do not have a "a seat at the table" for decision-making so decisions are made at a lower level (McKinsey&Co, 2013; Padilla & Kulkarni, 2012).
- **Organizational structure**. A senior leader is required to encourage and facilitate drug development due to his or her knowledge regarding pharmaceutical R&D. Another organizational change is outsourcing. The non-key capabilities can be outsourced to other companies specialized in those. Nevertheless, functions such as data analysis are key assets for the enterprise and should be developed in house (McKinsey&Co, 2013).
- Gain **flexibility** in research platforms and in portfolio management in order to stop the development of any molecule when they seem weak and at the same time, don't commit all the resources to one research platform.
- **Combine the required capabilities** for PMx development with the already existing and favour smaller-market drugs with a greater likelihood of success instead of bigger market drugs with lower success probability. With this approach change, companies will reap more benefits because of lower clinical costs, greater success rate and faster clinical trials.
- **Collaboration**: as explained in section 2.1 one pharmaceutical trend for the next 10-15 years is cross-collaboration. Sharing information with other companies and research centres will enable a faster development of drugs and a better understanding of diseases and diagnostic tests. Through strategic partnerships, companies will be able to get more value of their research and commercialization.
- **Sales force**: sales team need to be well informed to sale each drug's attributes and know to which patient segment they are targeted to and how the treatment works. Having an effective and completely knowledgeable sales force is a key asset to sell personalized medicine. What in the current drug system was an added value, in the case of personalized medicine is an essential attribute (Padilla & Kulkarni, 2012).
- **Talent supply:** there's a need to find people with both R&D skills and contact with other parts of the organization. These employers are needed to align biomarker research along in all

departments of the company. Also, there is a shortage of clinical knowledge and commercialization capabilities combined with R&D experience (McKinsey&Co, 2013).

3.7 Chapter Conclusions

When personalized medicine will directly be called medicine; that will be the moment when customized medicine becomes a reality: physicians will routinely write drug prescriptions that fit with each patient's needs (Lesko, 2007). In the future office visit, the doctor will make a prescription to the patient by not only checking his or her current health state but also examining the patient's genetic profile, monitoring tests and assessing his or her lifestyle. Computer-based algorithms will be used to determine the patient chances of suffering a specific chronic disease. By this mechanism, medicine will move from the current paradigm of being just reactive, to a preventive one. Modifying the patient's lifestyle and using prophylactics, the development of a chronic disease can be slowed down. Another possibility that is already growing is virtual doctor visits instead of direct patient-doctor contact. Patients will be more knowledgeable and active regarding their own healthcare (Ginsburg, & McCarthy, 2001).

Personalized medicine has developed a great hype but many steps forward need to be taken to make it a reality. In this section some requirements were pointed: the need for a different organizational structure with different and added capabilities plus a regulation that enhances the development and commercialization of diagnostic tests and drugs adjusted to patients' needs. Big pharmaceutical leaders and small start-ups are already embracing the new world of personalized medicine. However, there's still work to be done to overcome the resistance to change of the medical community. The completely change in the existing drug paradigm will require to reshape the business model for pharmaceutical drugs (Padilla & Kulkarni, 2012). As Christensen, et al. (2009) suggested, today's pharmaceutical leaders should educate themselves and adapt to this new trend in order to disrupt their own businesses and recap the benefits, as IBM did when introducing the personal PC.

CHAPTER 4: 3D PRINTING

After introducing the topic of personalized medicine, this section moves on to study a new manufacturing process that could enable the production of targeted medicines. Figure 12 shows the position of chapter 4 in the whole report.

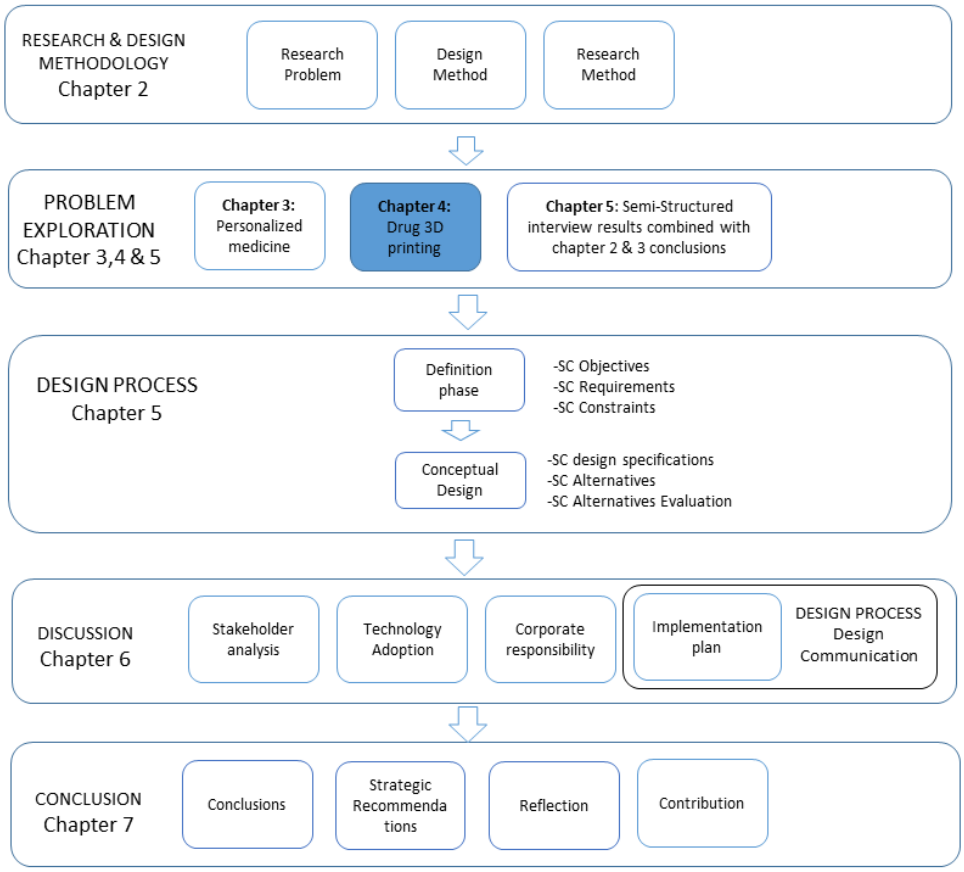

Figure 12 Position of Chapter 4 in the whole research framework. Source: this project

Until this point the need for personalized medicine has been shown but, why should 3D printing be considered to manufacture solid dosage forms? The first application could be to solve healthcare problems that could not be addressed otherwise (or at least not until the moment) such as lack of production routes for personalized medicines. Otherwise it could be used to enable distributed manufacturing, to manufacture stable formulations or to create multi-functional solid dosage forms (also called “polypills”). The technology behind 3D printing enables to fulfil these needs alone or in combination with traditional manufacturing processes (Roberts, 2016).

In this section the focus would be on drug 3D printing: its goals, the current techniques, the market value, the drugs that can be manufactured by this method, etc.

4.1 Additive manufacturing

Additive manufacturing, which is the industrialized version of 3D-printing, builds up components layer by layer until the final product is obtained. It uses powder formed materials that range from metals, plastics and composites. Additive manufacturing enables a design-driven manufacturing process; thus, it offers a high level of product customization and a serial production: exactly what's required for personalized medicine (Process, method and benefits, n.d.; Manners-Bell & Lyon, 2014). Additive manufacturing represents new realities for design businesses because they provide the unique chances of building exclusive complex geometries. But, not only that, with 3D printing it is possible to create one piece functional parts saving costs and time. Furthermore, it offers the reduction of waste creation and usage of harmful materials (Campbell, Williams, Ivanova, & Garrett, 2011).

Depending on the phase of the raw material used, many technologies do exist: solid-based 3D printing, liquid-based 3D printing and powder-based 3D printing (Karagol, n.d.).

4.2 3D printing

3D printers have been under development and application since 1980 and the perspectives are that soon they represent a major breakthrough for manufacturing as computers and the Internet did for information technology couple of years ago(Barnatt, n.d.; Jenkins et al., 2015).

This technology started in the niche of hobbyist and simple materials production. However, the latest developments over the past five years have shown that its impact is no longer restricted to that field. In 2014, this technology reached an estimated 44.1 billion of overall market size for printers, materials and services (Marchese, Crane, & Haley, 2015). The existing numerous and diverse applications of 3D printing technology range from consumable goods (like the Phillips customizable shaver) to 3D printed food that covers special alimentary needs and targets kid consumption (3D food printing: dichterbij dan menigeen denkt,2015; Millsaps, 2016). Other examples include prototyping, models, pieces or real objects (for example the first airplane manufactured almost fully via 3-D printing) (Dillow, 2011; "What is 3D printing? How does 3D printing work?," n.d.). But what has been done until now in the medical field? 3D printing usage is growing in this field by the fabrication of tailored prosthetics, medical implants, human tissues bio printing and organs and last but not least, novel drug formulations (3D printing for the industry, n.d.; Mills, 2015).

Current medical applications

One of the most promising applications is the case of organ printing due to the lack of compatibility between donors and the long transplant waiting lists. Its implications go beyond that, having very realistic organs could increase the reliability and effectiveness of drug testing and lower its economic and life costs (avoid animal trials). Another application that is already showing its potential is 3D printed prosthetics and orthopaedic implants. Printing photopolymers is becoming a cost-effective solution for prosthetics and orthopaedic implants such as hips, knees, spines and cranial implants that also offers patients more comfort as they are made according to their needs. Furthermore, these implants can be engineered adding patient's stem cells which made the implant more compatible and less probable to be rejected by the patient's body. Overall, the production by 3D printing enables the implant to function almost as it was part of the body. Another two fields of 3D printing success are hearing aids and dental implants. With

more than 10 million of 3D printed products in the market by the end of 2015, 3D printed hearing aids will sooner than later displace the hearing aids produced by current manufacturing methods (Berman, 2012; 3D Bioprinting: Medical Applications in 3D Printing, n.d.). And finally, the dental applications range from creating a 3D model of the oral cabity to help design dental restorations, to actually 3D print dental protesis (van Noort, 2012). The latest invetion regarding this application is a dental implant made with antimicrobial resin that kills harmful bacteria in the oral cavity (Dockrill, 2015).

4.3 Drug 3D printing

Currently, 3D printers are used to create prototypes and molds. However, this trend is changing and moving towards the production of final consumer products such as pharmaceutical drugs (Barnatt, n.d.). In this section the main points concerning drug 3D printing are covered: goals of drug 3D printing or also considered as market opportunities for drug 3D printing, techniques to 3D print drugs, company's position regarding this matter, requirements and challenges that drug 3D printing has to overcome to reach the mass market, etc.

4.3.1 Main goals of 3D printing medicine

Drug 3D printing poses at the same time a threat and an opportunity to pharmaceutical companies. On one side, current development pipeline of products is threatened because they are organized to produce large quantities of generically products on larger populations. However, this new model also poses opportunities for the companies as it embraces a market segment that was not covered until now. The main goal that this new manufacturing production has is: "Provide to the right patient, the right drug, the right dose at the right time". In order to achieve this, 3D printed medicine covers the following points:

- **Customer-specific drug production** versus current model of working generically on the whole population segment with a specific disease.
- **Enhance customer experiences (**more convenient systems to administer medicine and taste masked**)** (Aprecia pharmaceuticals, n.d.))
- **Flexibility on demand**: production is linked to customer demand (make-to-order production modes instead of make-to-stock) (Sandler, 2015).
- **New levels of structure:** polypills (many different pills combined into one).
- **New levels of dosage and release forms:** high dosages.
- **Cost effective and more environmental friendly production** (3D Bioprinting: Medical Applications in 3D Printing, n.d.)

4.3.2 Drug 3D printing: Current State

On August 3, 2015, the U.S. Food and Drug Administration approved Aprecia Pharmaceuticals SPRITAM® drug for the medication of epilepsy (Szczerba, 2015) (figure 13). The approval of the first drug produced by 3D printing opens up a new range of possibilities for customized medication, mislabelling, counterfeit drugs, changes in distribution and regulatory vacuum (Robinson, 2015). SPRITAM® is created with a porous structure that enables it to disperse in the mouth with just a sip of liquid. Its usage would be helpful for all those patients that have swallowing difficulties (from kids to patients that suffer from Alzheimer's or other neurologic diseases). A part from that, 3D printing enabled to concentrate a high dose into this drug (up to 1.000 mg) which solves a complicated trade-off between size and disperse speed (Crawford,

2015). The technology used and patented by Aprecia Pharmaceuticals is called **ZipDose®** and consists in stitching multiple layers of powdered medication together to form a porous and soluble matrix (Aprecia pharmaceuticals, n.d.).

Figure 13 Spritam® drug. Source: (Murphy, 2015).

Tailor-made medication targets patients who suffer high levels of side effects, whose genetic material requires special treatments to cure them (lack of a special enzyme that processes the commercial drug) or to treat illnesses that vary a lot between patients (mainly mental illnesses which require specific psychoactive drugs) (Miller, 2013). Apart from just genetic requirements, other environmental and epigenetic factors require tailored medicine. Those are for example: weight differences, percentage of body fat and age (children are more reluctant to take medicine, so colour and shape could be changed according to their preferences, see an example in figure 14). Also, rate of delivery (dissolve easily in the stomach), porous pills easier to swallow for taste-masked and convenient administration (like Spritam® drug from Aprecia pharmaceuticals) or to combine drugs together instead of taking numerous pills per day (for example, for elderly people) (Robinson, 2015). In figure 15 an example of a polypill developed for research purposes by the Laboratory of Biophysics and Surface Analysis of the University in Nottingham.

Figure 14 Examples of personalized 3D printed pills for children. Source: (University of Sussex, n.d.)

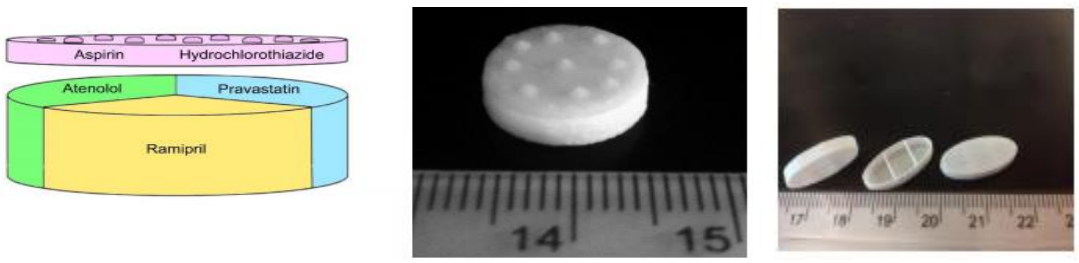

Figure 15 Multi-dosage pills (polypill). Source: (Roberts, 2016).

The implications of producing customized medicine for patients from pharmaceutical companies' point of view are: increase in production costs because of the small and more varied production for one single product that before. But, on the bright side, smaller and better targeted clinical trials due to the fact that the population to which the treatment is targeted is smaller too. However, the clinical trials are expensive even the population is smaller and a reduced target population causes diminished revenue potential (Miller, 2013).

Before going further, it is essential to assess whether all medicines could and would be produced by additive manufacturing or just some of them.

Existing techniques to produce 3D printed drugs

In this section first the type of printers that can be used for 3D printing and the techniques used to print drugs will be addressed.

Printers

From the range of 3D printers that do exist, such as fused deposition modeling (FDM), selective laser sistering (SLS) and stereolithography (SLA). The two most used printers for drug production are extrusion printers and inkjet.

Extrusion Printers: with the use of multiple nozzles they allow the production of multicomponent systems by melting the raw material and forming a continuous filament. After some research (according to Professor Clive Roberts), it has been demonstrated that extrusion 3D printing is a novel technique able to manufacture complex multi-drug (personalized) solid dosage forms with tailored drug release. Also, extrusion printers offer better flexibility and resolution. SPRITAM® was produced by this method (Roberts, 2016). Figure 16 shows a 3D printed drug by extrusion compared with a standard tablet.

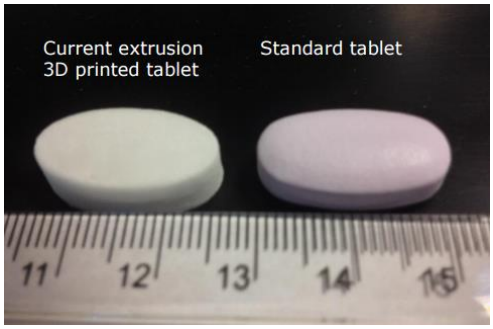

Figure 16 Comparison between a 3D printed tablet produced by extrusion method and a standard tablet. Source: (Roberts, 2016)

3D Ink-Jet printers (IJP) are regularly used in engineering applications for the manufacture of various polymeric and metal components. Compared with extrusion based system, this printer has an improved resolution and flexibility using APIS, binders and other in-active ingredients in the ink (Roberts, 2016). With these characteristics, Ink-jet printers allow to produce "theoretically" any type of dosage form and drug delivery systems. At the moment, the current usages of Ink-Jet printers are tissue engineering and regenerative medicine. To apply this type of printer for drug production, the required print head is similar to inkjet printer and also with multiple print heads it is possible to print multiple layers, which is suitable for 3D printing of oral dosage forms. Also, this type of printer uses the so called **drop-on-demand**

technology by which drops of ink are ejected, uniformly spaced and sized, with precision and accurate deposition and flexible dosing. Due to its accuracy, this system has great potential to produce low dose and personalized treatments (Erpelinck, 2016; Niklas, 2016).

According to Arnum (2014) and Ventola (2014) **Inkjet** and **powder-based printing** are the primary 3D printing technologies used for medicine development and production. The difference between them is whether powder or another material is used. Inkjet-based drug fabrication can be divided into two types of printing-based systems, continuous inkjet printing and drop-on-demand; in any case, inkjet printers spray formulations of medicines and binders in small droplets at specific speeds and sizes onto a substrate. Many different substrates are used, most commonly include different types of cellulose, paper, bio ceramics and glass scaffolds. Further improvements of this technology consists in spraying uniform "ink" droplets onto a liquid film that encapsulates it, obtaining micro particles and nanoparticles which could be used to distribute small hydrophobic molecules and growth factors. In powder-based 3D printing medicine fabrication, the inkjet printer sprays the "ink" onto the powder foundation. When the contact between them happens, the structure hardens and creates a solid dosage form, layer by layer. In drug production, a newly developed sub-type of inkjet technology called drop-on-demand (DOD) is used. This method locates active pharmaceutical ingredients (APIs) directly onto eatable substrates. When the droplets are ejected onto a solid layer of material, the DOD model has the name of **drop-on-solid deposition**. This system would allow to deposit a wide range of API onto a solid carrier (Jonathan, & Karim, 2016).

Drop wise additive manufacturing of pharmaceutical products can create high-potency drug forms, combination of drugs with multiple APIs or personalized medicine products tailored to a specific patient. This is due to the possibility of selecting which API to be deposited either in a solvent-based or polymer-melt based formulation and choosing as well which polymer is used in the formulation. The solvent-based formulation includes the API, a solvent and a polymer. A polymer-melt-based formulation is merely an API and a polymer, mixed and liquefied. Although this technique can be used for large-scale production of tablets, as shown by GlaxoSmithKline's Liquid Dispensing Technology, it is also considered as a viable alternative to produce either solvent-based or melt-based oral dosage forms (Hirshfield, Giridhar, Taylor, Harris, & Reklaitis, 2014). The advantages of Drop-on-demand technology are precise control over the material characteristics, drug form, size, and drop dynamics (Hirshfield et al., 2014; Ventola, 2014). The already mentioned SPRITAM® drug was produced following this methodology an approved for its commercialization in 2015 (Jonathan, & Karim, 2016).

By using this technology, it is also possible to fabricate **implantable devices** for the field of bone tissue engineering for example. In the case of pharmaceuticals, implantable devices could substitute oral drugs in for example, cancer therapy, chronic infectious diseases or for contraceptive therapies. 3D printing technology could solve problems such as lack of structural control and internal architecture at the same time that they can control the continuous release of the active ingredient for long periods of time (in vitro for 80 days) (Jonathan, & Karim, 2016).

A part from inkjet and extrusion systems, there also the **nozzle-based deposition systems** and laser-based systems. Regarding the first type, pharmaceuticals can be produced but the need for toxic organic solvents

arises a problem of instability and toxicology during manufacturing processes. Also, the need of this solvent would require an extra drying step to remove it (according to GMP requirements) adding costs at the same time that the API could be degraded. Another technique with possibilities is **fused-deposition modelling** in which a thermoplastic filament is extruded and later solidified. FDM technique is an attractive alternative to the drop-on-solid method as it can offer accurate dosing volume and release profile by developing different geometries. However, this technique has limited flexibility due to its low-dose thermostable API and the limited number of biodegradable polymers. And **laser-based writing systems** although it has been in the market since 1986 and it's widely used in bioengineering, has limited applicability in drug production. It is due mainly because its UV light exposure requirement to polymerize (and thus, FDA approved photosensitive polymers) and possible API degradation (Jonathan, & Karim, 2016).

A completely different 3D printer is the '**chemputer**' developed by Professor Lee Cronin, a chemist professor at Glasgow University, in 2012 which can perform the entire synthesis of any molecule (see figure 17). But not just that, the printer itself can produce, analyse and purify the drugs. This printer is not only capable of producing the containing structure but also the chemicals inside. Thus, without the need for specialized equipment, the chemputer has the potential to manufacture any drug needed (Sanderson, 2015). This technology develops new drugs at a molecular level by creating a 3D printed chemistry set from which a range of organic and inorganic compounds can be formed. These compounds can be programmed to make chemical reactions and produce different molecules (Juursema, 2015). The system consists in a software (computer-aided design, CAD) with which the molecules are designed, a hardware (3D printer), ink (a universal set of ink that can print everything) and a blueprint for the molecules to be printed. A blueprint is the organic chemistry behind that molecule that could be downloaded for a small fee or that could be essential to produce the molecule in the machine ensuring quality and compliance (Robinson, 2015). The process of printing consists in firstly, designing the molecule using CAD software. Once the design is completed, the file is sent to the 3D printer which deposits the material layer upon layer to create the finished material.

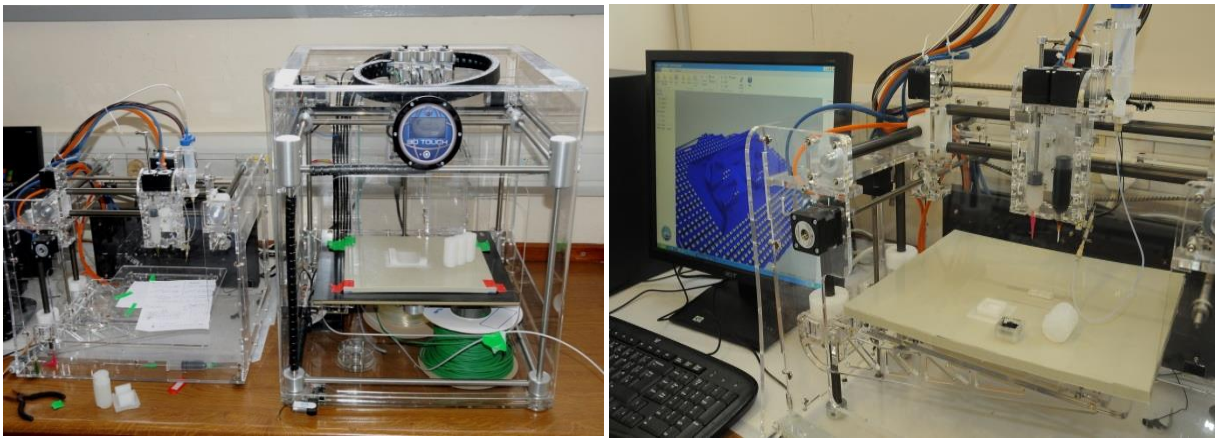

Figure 17 The "Chemputer" designed and produced by Lee Cronin. Source: left image (Germen, 2016), right image (Brandrick, 2012).

4.3.3 Market value

For pharmaceutical companies that are able to enter this new production market, there is the potential for mass applications of the technology. According to a published report by Vision Gain in 2014, the advance in production was predicted to be valued by more than $4 billion by 2018. There are also more implications for the pharmaceutical supply chain as 3D printing will allow medication to be factory-made closer to its end destination and thus, reducing logistic costs (Juursema, 2015). As stated in McKinsey Global Institute research report, the economic benefits of 3D printing regarding the manufacturing changes could represent up to **$550 billion a year by 2025** (Cohen, Sargeant, & Ken Somers, 2014).

4.3.4 Pharmaceutical drugs that can be 3D printed

Even though 3D printing can help to make the dream of personalized medicine become true, companies first need to determine which types of drugs may benefit from being 3D printed and then, what materials and software they may need(Juursema, 2015).

A spokesperson from the Medicine and Healthcare Products Agency claimed that in fact, 3D printing will change how the health service is right now. However, 3D printed drugs are more likely to **be personalized pills with a narrow therapeutic window** (such as oncology drugs) than conventional large-scale tablets like ibuprofen or aspirin (Juursema, 2015).

One of the most researched uses of 3D printing is the creation of drugs with complex drug-release profiles. Unlike the existing methods, with 3D printing a barrier between the active ingredients can be created to facilitate controlled drug release. For example, by printing on a matrix powder bed with differentiated layers or fabricate a complex porous geometry. Another usage of 3D printing are implantable drug delivery devices that can provide direct treatment to the area involved unlike the existing systemic medication. One example of application of this methodology are bone infections(Ventola, 2014).

According to the existing techniques available, the drug types that can be produced by 3D printing with the existing techniques are oral dosage forms (tablet or capsules) with the following structure: solvent, polymer and API or low-melting carriers (PEG compound and API)(Hirshfield et al., 2014). Capsules (the other type of enteral formulation) are not suited for 3D printing with the existing methods explained above. And parenteral formulations are not suited either because the idea of additive manufacturing doesn't yet consider the production of liquids. Figure 18 shows the production of a 3D printed tabled.

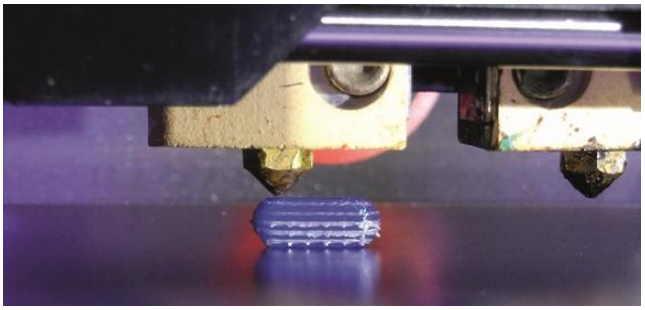

Figure 18 Production of a 3D printed tablet by printing layers of polymer with an API component inside. Source: (Sanderson, 2015)

3D Printing of oral drug forms offers freedom of design such as API distribution and dosage, tablet shape and structure as well as excipient use and distribution. The potential usages of the technology are:

- Production of oral dosage forms with varying dosages.
- Manufacture of oral dosage forms with specific release profiles.
- Easy fabrication of oral dosage forms with multiple APIs.
- Production of oral dosage forms with established internal structure.
- Manufacture of unique oral dosage forms shapes (Ventola, 2014).

As it has previously been explained with the case of Aprecia pharmaceutical's drug SPRITAM, 3D printing enables the production of high dosage pills. It has been predicted that by 2018, the market growth for high potent compounds is going to reach 10%. Given this growth and the possibility to target patient's need with 3D printing technology, more drugs similar to Spritam® are going to be introduced in the market soon (TNO working on personalized 3D printed oral dosage drugs, Steven Erpelinck reveals, 2016). A breakthrough like this will enable to produce the largest tablets in a fast melting format which provides a solution for all those patients with swallowing problems (Crawford, 2015). So far the technology based on drop-on-demand and drop-on-solid used to manufacture SPRITAM® seemed not to interest pharmaceutical companies; however, with the commercialization of this first drug, a new path will open. On the other hand, for implantable systems such as the ones explained in the section above, this technology really makes a difference and seems that the products manufactured in this way will more likely, at least in a shorter term, be seen in the market (Jonathan, & Karim, 2016).

One thing is what is promised that a technology could do, and another completely different is what it can actually do. So, what ink formulations have been tried in 3D printing of drugs? According to Ventola (2014), ink formulations have included a variety of active and inactive ingredients. In the first case, the ingredients tried varied from small molecules like caffeine to other more complicated such as steroidal anti-inflammatory drugs, acetaminophen, vancomycin, ofloxacin, dexamethasone, paclitaxel and folic acid as few examples. Inactive ingredients tried in 3D print drugs were: poly (lactic-glycolic acid), cellulose, ethanol-dimethyl sulfide, glycerin, surfactants, propylene glycol, acetone, methanol as few examples.

However, more research is required to find the right materials to manufacture tablets with varying dosages. Dr. Ricky Wildman from University of Nottingham (UK) is looking at which materials could be used for inkjet 3D printing. He recognizes that for real applications the world would have to wait possibly 5 to 10 or even 15 years (Sanderson, 2015).

From the Top 10 list of the best-selling drugs in the US published in May 2015, 5 of them were tablets that could be 3D printed in the near future as envisioned by Sanderson (2015). To give some examples, Abilify from Otsuka Pharmaceutical which is an antipsychotic medication, two hepatitis C medication Sovaldi from Gilead Science and Harvoni from Gilead, Crestor from AstraZeneca, a cholesterol-lowering drug and the proton pump inhibitor Nexium from AstraZeneca as well. If their market sales in the US are summed, the value reaches $61 billion. Furthermore, about two-thirds of all prescriptions nowadays are dispensed as compact dosage formulas (the ones that could be 3D printed), and half of these are compressed tablets (Dosage Form Enablers, n.d.; Palmer, 2015).

Another possibility of **oral drug** design is the use of thin **films** of the size of a stamp (see figure 19). The dispersion method consists in placing the mediation in the mouth and then it is diluted. Some products that already exist in the market are against sore throat and nasal congestion or constipation. This production design allows to distribute the API or different APIs into different layers. If these drugs were mass produced, the usage of a 3D printer would delete one step of the manufacturing process: firstly, the basic film would be produced and then, the active ingredients would be disposed on it. The location of the API in different positions on the film and many layers, establishes different release patterns and also serialization and barcode printing to identify the drugs and avoid counterfeiting. The application of 3D printing for the production of oral films is the same as the other oral drugs: treatment personalization. And the advantages are the same: improve patients' compliance with prescriptions, supply correct dosages for children and elderly and combining more than one drug into one. Furthermore, this system, by printing multiple drugs separated in the same film, reduces stability issues and incompatibilities between those substances (Preis, Breitkreutz, & Sandler, 2015).

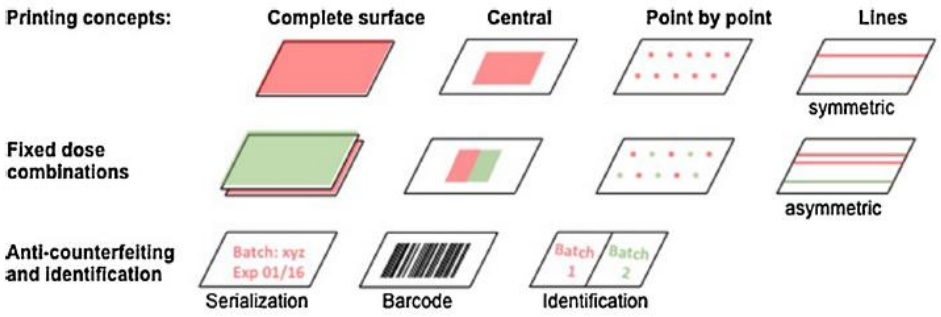

Figure 19 Oral drug production in films. In the first line it's clearly seen the different printing position of the drugs so the release profile can be organized. In the second line, a part from organizing the different positions, it is shown how different combinations of drugs could be arranged. And finally, the third row shows barcoding and serialization as anti-counterfeiting techniques. Source: (Preis et al., 2015).

Another topic of interest is to check how expiration dates for medicine will change or be effected by 3D printing them. This will be further developed in section 4.3.6.

4.3.5 Companies already producing 3D printed drugs

The past years, the concept of 3D printing has attracted the attention of a number of academics and pharmaceutical companies. In the UK, Dr. Stephen Hilton from the University College of London founded **FabRx in 2014.** This company develops 3D printed drugs, as well as other forms of modified release tablets (Juursema, 2015). Also, as already mentioned in the beginning of this section, **Aprecia Pharmaceuticals** is a US company that produces drugs by using 3D printing technology. They have developed the ZipDose technology which enables the production of 3D printed drugs that are easy to take. Aprecia produced the first 3D printed drug approved by the FDA and they have many similar drugs in their pipeline (Aprecia pharmaceuticals, n.d.).

Not only small start-ups are interested in 3DP, big Pharmaceutical giants like **GlaxoSmithKline** are running R&D projects looking at drugs that could be 3D printed (Juursema, 2015). Other big pharmaceutical leaders such as **Pfizer, Roche and AstraZeneca** are focusing their R&D resources in researching new

biomarkers and pharmagenomics. They are not directly developing new drugs by 3D printing but still in the field of personalized medicine.

4.3.6 Requirements

Until this point, the techniques to produce 3D printed drugs, the type of drugs to be produced and company's position regarding this breakthrough technology have been explained in depth. However, drug 3D printing to become a reality and adopted by the drug production community, few requirements need to be solved.

Routine production

What are the requirements to adopt drug 3D printing in a mass production scale?

Will be a printer for each product or the same printer will produce many products? If so, how that could be achieved? The answer to this point is necessary to establish the investments required to produce drugs by 3D printing in a large scale (pharmacies or hospitals that have many patients daily). Many concerns depart from this problem: if many products are produced by the same printer, how quality will be ensured? Will the printer be cleaned after each use or some pieces of it will be exchanged after each use?

How will this new production be integrated in the production line (packaging, etc.)? if the printer produces personalized drugs for one single patient each time it could be that after printing, the drugs will be delivered to the patient in a small bag. But, if they are used in mass production of tablets, it would be required packaging in blisters for example, how that would be integrated?

Maintenance (cleaning, faults, etc.): this point is related to the first one, how will the printer be cleaned and when will it be necessary? And how faults will be avoided? If each customer has a printer at home, how regulatory agencies and the government could control the production of those and avoid fraud?

Efficiency (cost of goods). What would the efficiency of 3D printers be? How much would the products costs and how that would affect healthcare costs? The expectations are that drug 3D printing will lower healthcare costs by targeting treatments (lower the number of non-effective treatments, shorten the treatment time).

Scale-up feasibility: how will this production method produce enough products to supply a medium to large number of customers? Will be many printers positioned in line and manufacture 24h per day 7 days per week? Would a lower production be required?

GMP requirements: another point of both interest and concern is whether the current GMP could be applied to all production methods or if any changes would be necessary (Crawford, 2015).

Will this **production method be competitive to conventional cost of goods**? The answer to this question will determine which type of products are produced by 3D printing, if it will complement the current mass production system by producing personalized products or if it will change completely the paradigm.

How **reproducibility** will be ensured? This regards to the API composition mainly. How can it be ensured that the quantity of API will be the required each time and also of the necessary volume? By using inject

technology, multiple pills can be produced in a single manufacturing process with a very good reproducibility (lower than 1-2%w) but with some variations between batches (Erpelinck, 2016).

The source of this section, if not written otherwise was Shang, 2016.

Pharmaceutical development: Formulation

Another area of concern is medicines' formulation. Which **excipients** could be used with 3D printing technology? how **compatibility** could be ensured between APIs and excipients? API's morphology, what would be **stability** and **dissolution** of these products? Both aspects are essential to establish quality and expiration date (Shang, 2016; Erpelinck, 2016).

One solution to ensure **quality** and **safety** is a digital rights management approach by which it will prevent printers from recognizing 3D files for illicit drugs. However, as we know from experience, it has not worked well for the entertainment industry (from movies and music to console games) (Ventola, 2014). To ensure product's quality, according to Dr. Alhnan, pharmaceutical researcher at the University of Central Lancashire (in Preston), printed medicines would need to be produced under the supervision of someone with a license to operate a 3D printer to dispense drugs. Furthermore, regulators need to know that the printers give the same product every time. To ensure this, an in-line system of analysing layer by layer of the drug is required (Sanderson, 2015). Serialization and barcode printing has already been mentioned before in the production of oral drugs printed in films in the article by (Preis et al., 2015). Also, regarding safety and quality, it is mentioned in the same article that isolation of the printing station could be advantageous within at least, high potent drugs.

Another point is that multi-API drugs (already mentioned as a new possibility that this technology opens) are not "liked" by regulators. This is because the interactions between drugs are not clear and the dispersion through the body is less controlled (Shang, 2016).

The **expiration date** refers to the last day that the producer guarantees the complete safety and potency of a drug. After this date, manufacturers are not liable for the side effects or non-effect that the drug may have caused. The number of days the drug can be used after fabrication is dependent upon the drug ingredients (API and polymers used to build the pills) and storage conditions. The main disturbing conditions are temperature oscillations, light and moisture. The most stable medication types are capsules and pills; whereas drugs that do exist in solution such as injectable drugs have shorter life cycles (Anderson, 2014). (more information Appendix A) The main concern regarding 3D printed drugs is how expiration date would be determined. Would it be established as now, giving an x number of days after production or would medicine expire just after they are produced so instant consumption would be required?

Regulation

Regulation is an umbrella term for many concerns regarding 3D printing: patent and copyright concerns, privacy and confidentiality of the data, regulators' requirements, drug liability and safety and security terms.

Patent and copyright concerns: 3D printing raises huge concerns regarding intellectual property rights (IPR) due to its capabilities to recreate any object. Until now, pharmaceutical companies, by patenting were provided with 20 years of protection against reproduction and commercialization of their products; however, with 3D printing the whole landscape could change. Not only firms, but also individuals could duplicate their products easily (Karagol, n.d.). In the past, manufacturing applications of 3D printing have been subject to copyright, patent, industrial design and trademark law. Nonetheless, it is not known how these laws should apply to the use of 3D printing for personal use, commercial sale or non-profit distribution. If an individual want to distribute a 3D-printed version of a patented item, that person needs to negotiate a license with the patent owner, because the distribution of the item without permission would violate patent law. In addition, it will be very challenging for companies to find and prove any violations to IPR codes (Hornick & Roland, 2013).

Although copyrights traditionally don't apply to functional objects, they do have an importance in 3D printing. For example, in at least one case, a designer filed a copyright takedown notice because he considered the design to infringe on his copyright (Ventola, 2014).

The "digital blueprint" used in 3D printing can be obtained from an existent CAD file or newly acquired by using a 3D scanner that generates a digital image of the object. CAD files are protected by the existing laws and regulations in a way that it is forbidden to use them without author's consent. In the other case, if a person uses a 3D scanner and creates and image of the object and then a blueprint of it, if the parts copied are unprotected, he or she will not be liable for copyright infringement. However, the person will not escape from patent infringement when the product is produced, sold or used (Davies, et al. 2014), 2014).

Trademarks such as brand names and logos are used to protect owners against appropriation of their creations at the same time that they do protect consumers from confusion created when different products use similar marks as others. In the case of 3D printers, trademarks help to protect a manufacturer from counterfeiting when the printer includes the manufacturer's mark on each produced product (Davies, et al. 2014).

Moreover, of great importance is the question of **privacy, confidentiality and ownership** of the data obtained in the genetic tests and past health issues required to develop the personalized medicine. Many people have significant worries that this information could be used against them by insurance companies for example by increasing premiums or even deny coverage (Johnson & Johnson Pharmaceutical Research and Development, 2011). Nevertheless, the data should be protected in the same way as the current systems by a written agreement with all processors (Vijverman, 2016).

And last but not least, ensuring **approval from regulators** is another significant barrier that may impede the widespread drug production by 3D printing. There are two main branches regarding regulation, the regulatory aspects concerning bringing manufacturing closer to the patient and the regulatory perspective of flexible manufacturing. From the first branch, regulators require that drug 3D printers must also be legally defined as manufacturing or compounding equipment and be then subject to those laws. And from the second branch, regulators will require that flexibility in terms of manufacturing is defined and all

possibilities considered in the regulation (Ventola, 2014). At the moment, there's no clear legislation covering 3D printed products such as drugs separated from "old style" medicinal products (Vijverman, 2016).

Regarding both branches, FDA is considering the following technical aspects to develop a new regulation for 3D printing: **pre-printing considerations** (mostly about materials used: properties and recyclability; and from the process: validation and reproducibility); **printing considerations** (process characterization and software required) and **post-printing considerations** (cleaning, sterilization, biocompatibility, verification, etc.)(Davies, et al. 2014).

Another essential policy requirement is **liability** implications for defective drugs. Liable is understood as the obligation that the person who is engaged in selling or distributing defective products has with anyone that has been harmed by his or her products due to a defect on them. In the case of 3D printers, a concern arises: who will be liable? The medical device producer, ingredients producers or distributors, the person or the organization doing the printing?(Robinson, 2015). How will the traditional terms of liability, warranties and negligence apply in this case? There are different possible case alternatives: "(1) defective original product used to create the digital design; (2) defective original digital design; (3) defective digital file; (4) corrupted copy of downloaded digital file; (5) defective 3D printer; (6) defective bulk printing material used in 3D printer; (7) human error in implementing the digital design; and (8) human error in using the 3D printer and/or materials. Product end users seeking to recover from side effects resulting from a 3D printed product could be left wondering: who is liable?" (Billam, n.d, p. 4). Under the current regulation, hospitals are seen as service providers not as product sellers as they are not under the commercial sphere. However, will the production in site of drugs by 3D printing affect the way that they are considered? Will they be considered as "manufacturers" in terms of liability or negligence? Nevertheless, unless the manufacturer has freedom to change any of the production terms (materials, recipe, and combination), it is unlikely that they are held responsible for a defective product (Davies, et al. 2014).

Lastly, 3D printing of drugs has already raised concerns about **safety and security**. Additive manufacturing has opened up opportunities for customers to evade the rules. For example, printing illegal items like guns or master keys. In the field of producing pharmaceuticals, without any official standards or regulation, the blueprints and inks could be mislabelled. But not just that, also the software could be hacked and cause extremely harmful consequences for patients(Le, 2013). Thus, all 3D printing production methods need to be properly controlled so that the quality of the products can be assured to patients and healthcare professionals(Juursema, 2015).

The ability to change each product and make it unique will allow for example to print individual barcodes in each pill, this could be used to ensure traceability of the products (link the recipe to produce an individual pill to the specific printed pill) (see figure 20) (University of Sussex, n.d.).

Figure 20 . Barcode printed on a printed pill. Source: (University of Sussex, n.d.)

With the current distribution concept, the products move from the manufacture to the wholesaler and then they are sold in the pharmacy; thus, through all the process the medicine is controlled and delivered to the patient after been tested by a qualified person for compliance with specifications. However, in the new model that drug 3D printing is suggesting, how can quality be ensured during the manufacturing process? And how the quality will be tracked for liability and safety? (Shang, 2016).

Personalized medicine offers a wide range of potential benefits to consumers. Basically, an improved ability to select optimum treatment regimens and by doing this, reduce trial and error prescribing practices. A better understanding of pharmacogenomics should lead to the development of safer dosing options, helping to reduce adverse drug effects and tolerability issues. Therefore, answers and solutions to the concerns above are required to exploit the possibilities for personalized medicine produced by 3D printing in the future (Johnson & Johnson Pharmaceutical Research and Development, 2011).

Limitations of 3D printing technology

In order to allow high volume production, 3D printing speed has to improve and materials have to lower the price and become more diversified to allow the production of any drug possible. The type of material used is of extremely importance in drug manufacturing as complex molecules are required (Cohen, Sargeant & Somers, 2014).

Another limitation are 3D printer prices. In the near future prices will remain steady or rise due to the introduction of new features. But new entrants in Asia and patent expirations will put pressure to lower prices. Also, material rates ought to decrease due to the continuously development of new materials, the appearance of new suppliers and the increase in demand (Cohen, George & Shaw, 2015).

Regarding technological limitations, 3D printing is less accurate than traditional manufacturing and operational expenses are high (powder and materials). To enable mass customization, larger and faster printers and new materials would be required. In the last years, there's been massive improvements regarding printers' possibilities but there's still a long path until drugs would be manufactured by this technique (Manyika et al., 2012).

The players that understand and overcome these limitations will be the ones to get the highest market share. Some of the key industry players are already creating centres of research and development and hiring experts in the field of additive manufacturing (Cohen, Sargeant & Somers, 2014).

Another point of concern is the printing time required to produce a conventional tablet. Using the current techniques, this time is 2h and 12 minutes. Although this production time has decreased lately, it is far longer than the conventional tableting processes which produce 15000 tablets per minute. At this current production timing, drug 3D printing is more suitable to be used in pre-development stages or clinical studies in which dosage can be adjusted to animals' weight and therapeutic dose; or in pre development where it could be useful to validate pre formulations (Jonathan, & Karim, 2016).

Complementary technologies

According to the American Society for testing and Materials, there are 4 main techniques and processes required to perform 3D printing: hardware (apart from the 3D printer), software, materials and Big data (3D Bioprinting: Medical Applications in 3D Printing, n.d.).

Design software

As already mentioned before, the first step before 3D printing an object is designing the object itself (either as doing it from scratch, scanning the real object or downloading a current design). No matter what is the source of the design, it will be required to convert it into an industry-standard ".STL" file and before printing, another software could be used to check for errors and topology optimization (3D Bioprinting: Medical Applications in 3D Printing, n.d.).

3D scanners (as hardware)

In the case of drug 3D printing, the need for precise and reliable scanners is not really necessary as happens in other applications because for this specific application, to produce a 3D printed drug it is required to copy the composition of the drug, not the external structure.

Material science

In order to enable all the possible applications that 3D printing offers in theory, the development of new materials is essential. By 2019, it is expected a growth of 18% in the filaments market. Not only that, the research and development of new ceramics and metals and small molecules and polymers in the case of drug 3D printing will increase as well. The investment on materials represents nearly the 50% of the whole expenditure by automotive, dental and medical industries that use 3D printing as a production method (3D Bioprinting: Medical Applications in 3D Printing, n.d.).

Future trends in materials that could be used in the future for 3D printing are **BioInks** (which contain living cells) **and Biopolymers** (in dentistry for example). There are many types of bioInks, from the ones researched at the moment, the most promising ones are gelatin-based inks, vascular inks and stem cell inks. However, their application will be most likely into tissue development rather than drugs.

Big data

Data and analytics are the midpoint of the new personalized drug manufacture. Not only large amounts of data need to be acquired, but also analytic tools to process and store all this data and display it when it's necessary.

Lately, the healthcare system has experienced a tremendous increase in information flow. "Diagnostic images, genetic test results and biometric information are increasingly generated and stored in electronic

health records presenting us with challenges in data that is by nature high volume, variety and velocity, thereby necessitating novel ways to store, manage and process big data" (Panahiazar et al., 2014, p.790). In order to create personalized medicine, all this data needs to be analysed to generate medical insights. Furthermore, to target a drug to a specific patient, physicians need to understand the disease cause and its behaviour; to do so, it is necessary to combine information coming from -omics, clinical-trials and patients' clinical data. Therefore, an infrastructure to collect and store all that data plus the analytical methods that analyse it are required (Panahiazar et al.,2014).

It is not just about gathering and tracking large volumes of data, manufacturers have to review all that data and use it to correlate with what the patient experiences; in this way, drug producers can ensure that the intended drug effect is what the patient experiences and not side effects as an example. Some manufacturers have already established consortiums in which partnering with other companies and laboratories they analyse and correlate this real patients' data with drug usage.

As estimated by the McKinsey Global institute, big data could generate an amount up to $100 billion of annual value by providing data to optimize innovation, improve efficiency in research and development and generating new tools for physicians, patients and pharmaceutical companies to provide a personalized healthcare (Cattell, Chilukuri, & Levy, 2013). In this way, big data will drive down both healthcare and production costs and increase patient security (Davis, 2012).

To further read about several challenges regarding data processing, analysis, data integration, etc. go to Appendix Part A Big data.

4.4 Chapter Conclusions

Scientists like Clive Roberts and companies such as Aprecia Pharmaceuticals have proven that 3D printing of drugs is a reality. The mass-market production of those depends on fulfilling the technical requirements such as standards to ensure safety and quality and solving legal and liability challenges. The possibilities that this opens are unlimited and that brings a new paradigm: from all the possibilities, which of those are the most probable to actually develop? Where will be the 3D printers located? And which products will be actually produced by 3D printing? The answers to these questions will determine the path that drug 3D printing will take in the short and long term. Accordingly, Spritam® has created the precedent for a short or long term 3D printed personalized drug production; however, in order to be mass produced, the research carried in the upcoming months and years need to provide solutions to all those requirements explained in depth in section 5.3: regulation, pharmaceutical development and complementary technologies such as new materials and big data need to be further developed to enable the promised: "a future of tailored medication for each patient".

CHAPTER 5. DRUG 3D PRINTING IN PHARMACEUTICAL LOGISTICS

In this chapter, the results of the exploration phase which included semi structured interviews and the literature review are presented. In a second sub section, those results are combined to develop the design requirements that will led to the re-design of the different supply chain alternatives using the SCOR model. The last step of the design process, the implementation plan is included in the next chapter because to provide the implementation strategy of 3D printing in the pharmaceutical supply chain, other inputs are required (such as the ones explained in chapter 6). Figure 21 shows the position of chapter 5 in the whole report.

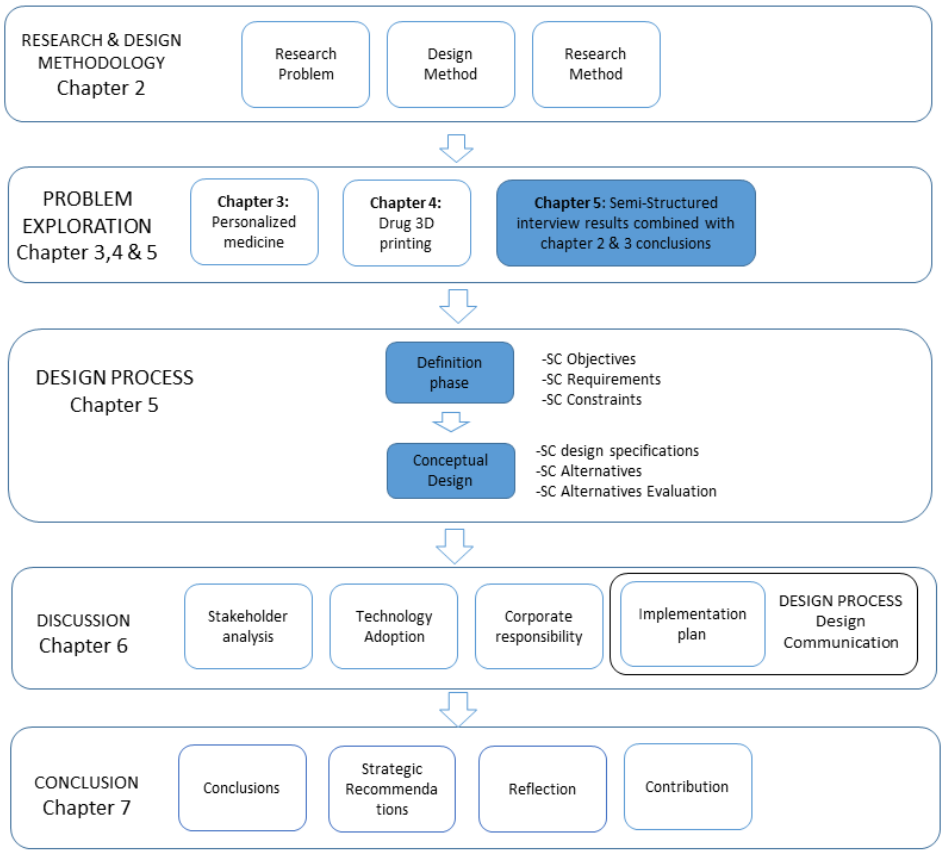

Figure 21 Position of Chapter 5 in the whole research framework. Source: this project

5.1. Literature review conclusions

Based on the literature review and the knowledge gap presented in chapter 3 and 4, a conceptual map of the relationships that pharmaceutical challenges, 3D printing and personalized medicine have (see figure 22). With this map, a clearer explanation of why **drug 3D printing and personalized medicine would be considered as two terms that have to be combined** in order to fulfil customers' and industry needs.

In the model shown in figure 22 the three main concepts researched in this literature review: pharmaceutical field (chapter 2 under research problem), personalized medicine (chapter 3) and 3D printing (chapter 4) are linked together. By producing drugs using 3D printing technique the existing challenges of the pharmaceutical field are overcome (low productivity, need for personalized medication,

huge inventories, stock outs) and a production method to obtain personalized medicine is offered. The main benefits of drug 3D printing are tailor-made production, satisfy the customers and produce new drugs. Furthermore, by sending the production closer to customers, the Supply chain becomes more efficient and lower inventory levels are needed.

In the second part of chapter 5, the main requirements and design specifications that the supply chain needs to fulfil to enable the production of drugs by 3D printing would be used to re-design the pharmaceutical supply chain.

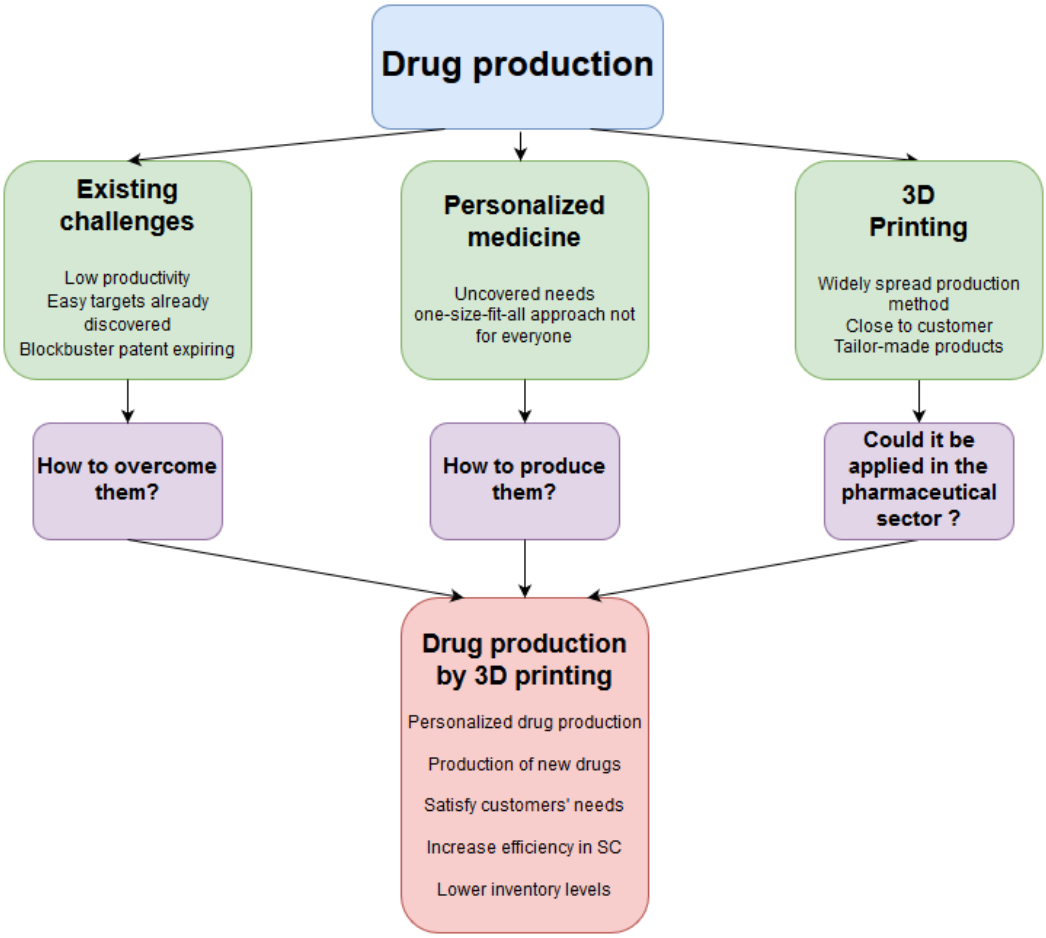

Figure 22 Theoretical framework conceptual model. Source: this project.

5.2. Impacts of drug 3D printing on the pharmaceutical supply chain

In this section the requirements, specifications are constraints necessary to re design pharmaceutical supply chain when 3D printing is used as a production process will be extensively explained and analysed. At the same time, the challenges and supply chain opportunities will be also pointed. The data used for this is a mixture of the literature review in chapter 3 and 4 and the expert interviews. The first sub section is divided upon initial findings, 3D printer positioning, drug 3D printing benefits and business strategy. And the second sub section comprises the design process to obtain the different supply chain alternatvies.

The key interview findings presented in this section have been developed more in depth in the Appendix Part B under the title interview analysis.

5.2.1. Initial findings

After analysing each group of interviews, the findings are depictured in issue maps (figures 23-26) in order to analyse actor by actor the topics that were discussed in the interviews. Also, they are used to see the interrelations between topics and to highlight the most important issues. Each map shows the interviewee and the key words that he mentioned in the discussion plus the ideas that he pointed regarding that key word (the coding process to obtain the key words is explained in section 2.4.2 and the process is included in the appendix part B interview analysis). For example, in the first issue map (figure 23), when discussed about type of medicines, drugs with small therapy window were pointed. The article from Bryson (2004) in which the technique of stakeholder-issue interrelationship diagrams used to identify and analyse the stakeholders' interests and the interrelations between them.

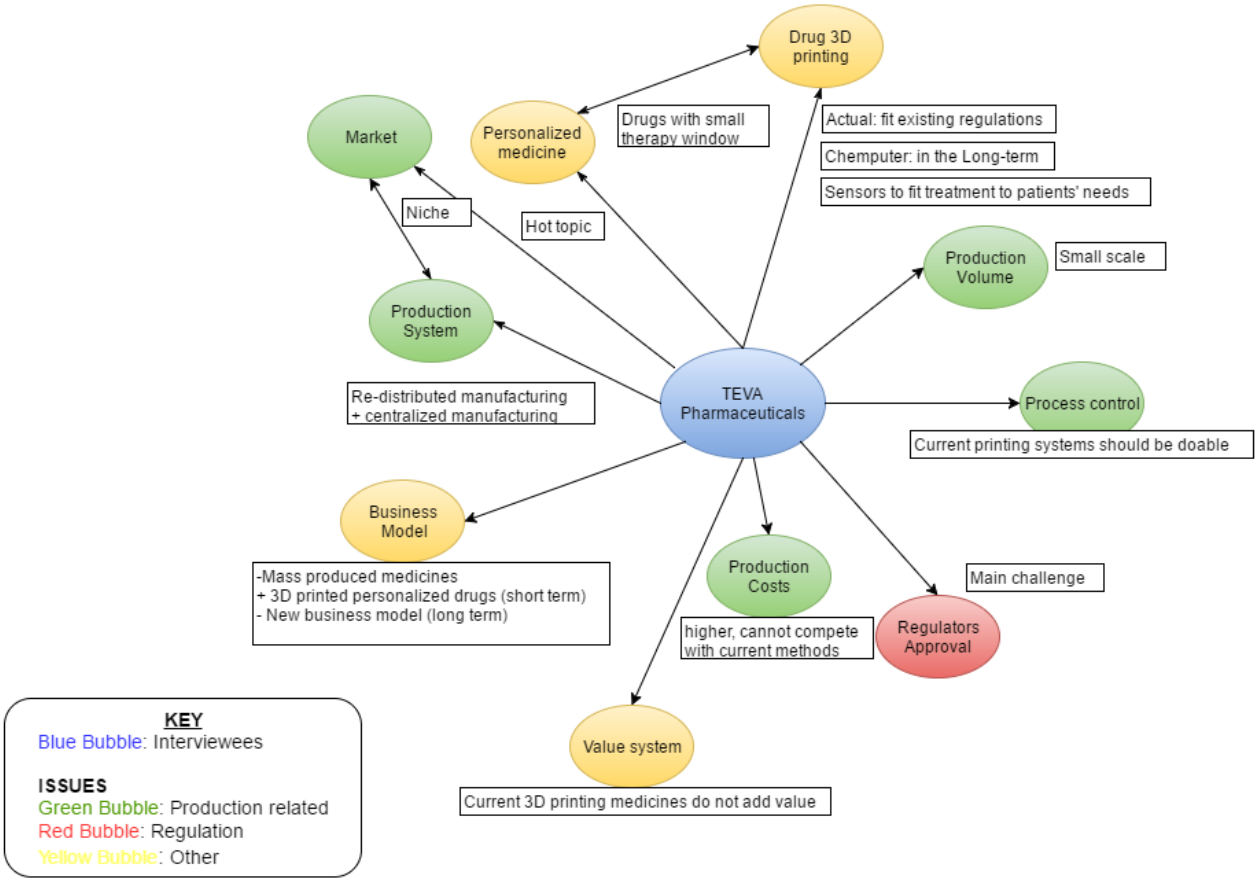

Figure 23 Pharmaceutical company expert interview results shown in an issue map. Source: this project

In the case of pharmaceutical expert's opinion (figure 23), the results are classified into production related, regulation and business related. In the production related section, medicine types, costs and production volume are highlighted. In terms of regulation, the main concerns are safety and regulation approval. And market opportunity, additional value, profits, business model employed, company's strategy and market dynamics are the main findings in the business related section.

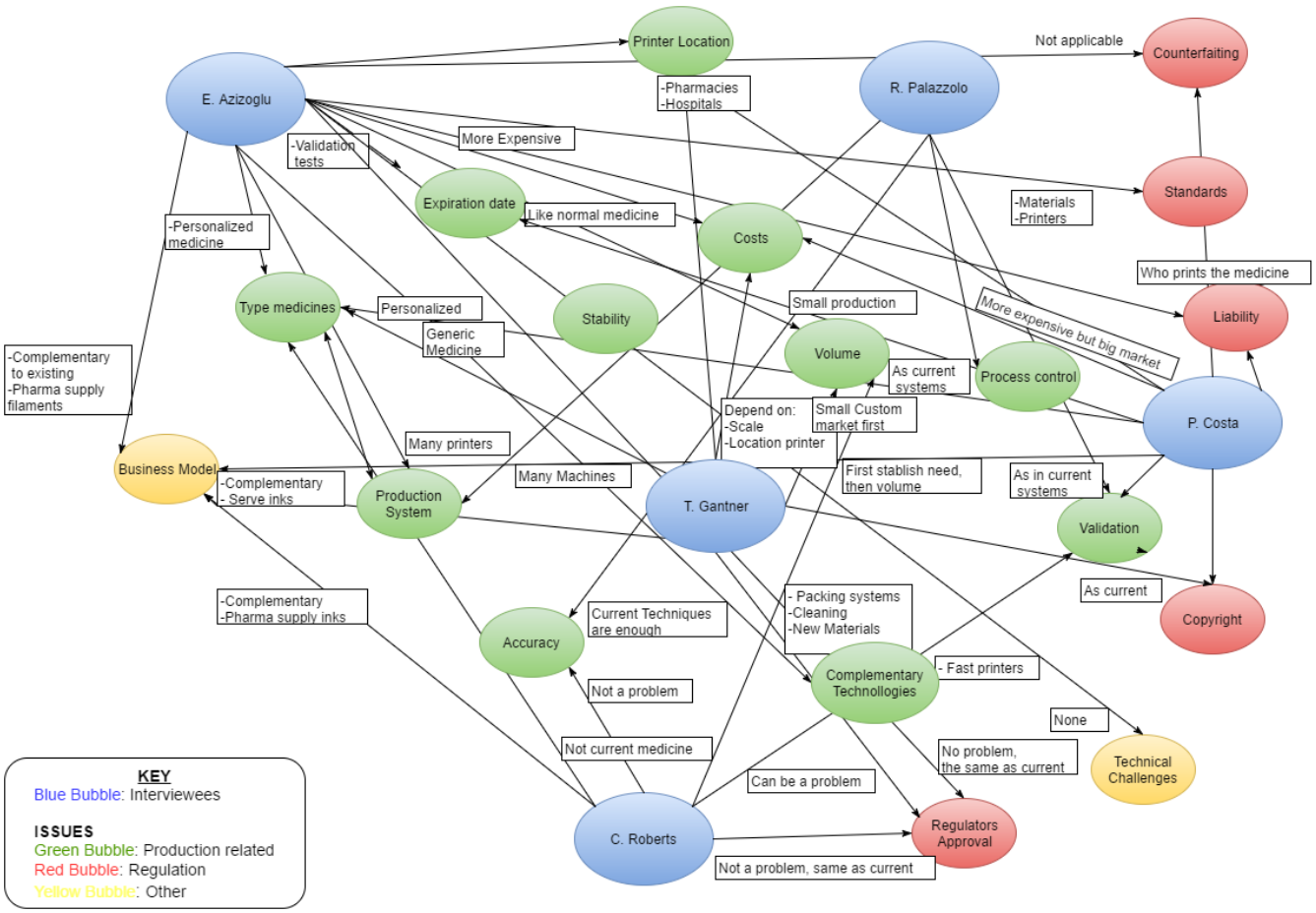

Figure 24 3D printing experts interview results shown in an issue map. Source: this project

Generalizing the results of each actor, the main findings of 3D printing experts' interviews shown in figure 24 are classified into: production matters, regulation and others. Regarding production, the key elements are expiration date, stability of the medicines, type of medicines produced, production systems, printer location and production volume. Regulatory concerns refer to gaining regulator's approval and others refer to the business model used to produce and commercialize the medicines.

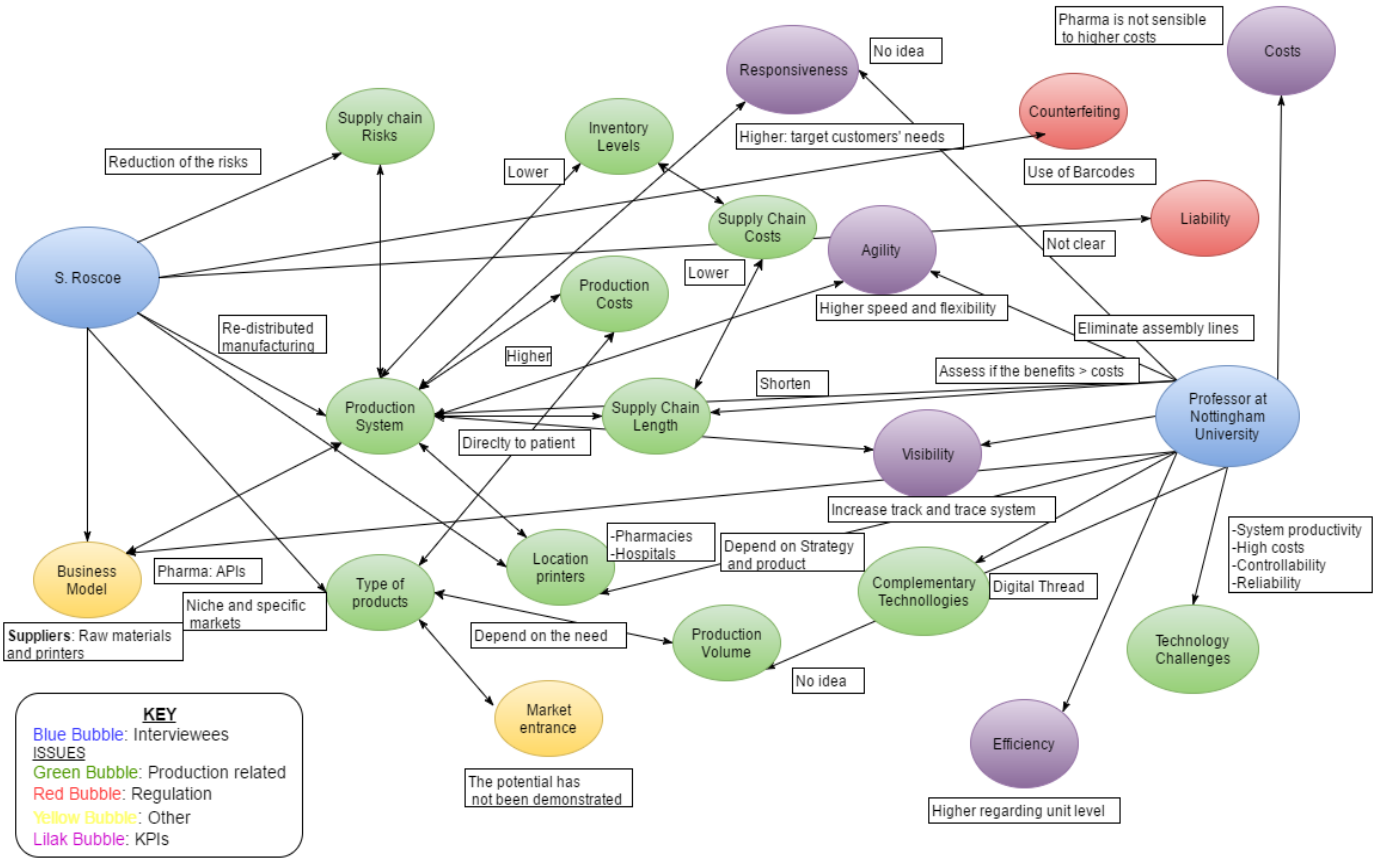

Figure 25 Supply Chain experts interview results shown in an issue map. Source: this project

The supply chain experts' results (figure 25) are grouped into production related terms, regulation, KPIs and others. Related to manufacturing, the key points discussed were production system, production volume, printer location, technology challenges and type of products. Related to supply chain, length and costs were pointed as key elements together with responsiveness, agility and efficiency. Also, the business model employed to produce and commercialize the medicines was mentioned.

And finally, the fourth group of interviewees, the regulatory experts' panel pointed the production system used, production costs, medicine types, GMP, quality, safety, standards, process and product qualification, traceability and counterfeiting. See figure 26 for further details.

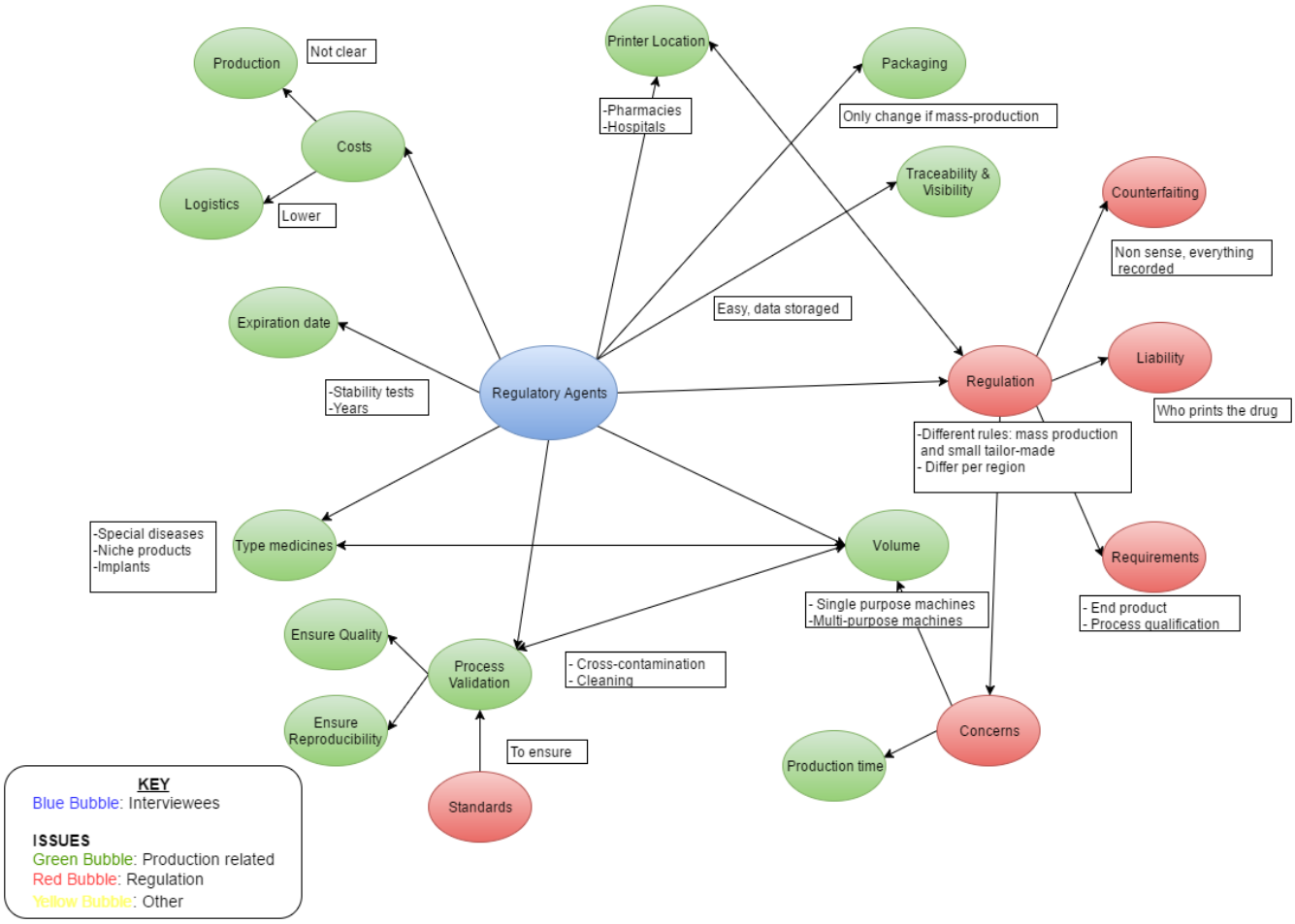

Figure 26 Supply Chain experts interview results shown in an issue map. Source: this project

A detailed analysis of each group of interviewees is shown in Appendix B under the title interview analysis in which a classification of all topics covered and key words are provided with percentages of appearance.

From the issue maps of each group of interviewees (figure 23-26), another issue map is obtained showing all the interconnections (see figure 27). The most important interconnections will be pointed in this explanation. The **type of medicines** is interconnected with **the business model**, **the production costs, the production system and the production volume**. The production costs and volume are at the same time interconnected. This is because depending the drugs produced and commercialized, the strategy would differ and so would the business model and the costs to produce them. In terms of strategy and costs, it is not the same to mass produce medicines such as ibuprofen or aspirin or to specialize in personalized medicine which market is smaller and more demanding. In this case, the demand is lower with higher production costs but the selling prices are higher too. Also, the medicine type is connected with the production volume as already explained and this is connected with the production cost. Depending on the production system, the manufacture point would differ (printer position), the type of medicines produced, the business model and the supply chain. The main supply chain effects are on its costs due to change of length (not only this) and supply chain risks. If the production follows the centralized model, the location of the 3D printer would be at the main manufacture point such as now, but if it is a de centralized model,

the location could be from the warehouse to each patient's home. The production system used would directly affect the **inventory levels** and the **supply chain's lengths** and **risks**. A de centralized model needs less inventory and shorter supply chain as it is closer to customer which reduces risks as demand is more predictable. Supply chain length and inventory level (higher inventory needs bigger or more numerous warehouses) directly affect the costs and the key supply chain performance indicators: **agility, efficiency, visibility and responsiveness**. For example, lower inventory levels increase the supply chain's agility and efficiency which are also affected by supply chains length. Efficiency is altered by the inventory levels, costs and supply chain lengths. Visibility, though, is mainly affected by the length of the supply chain. And responsiveness, is due to the length of the logistics part and the production system used. As already explained and shown in figure 27, the Key performance indicators are directly affected by the supply chain effects.

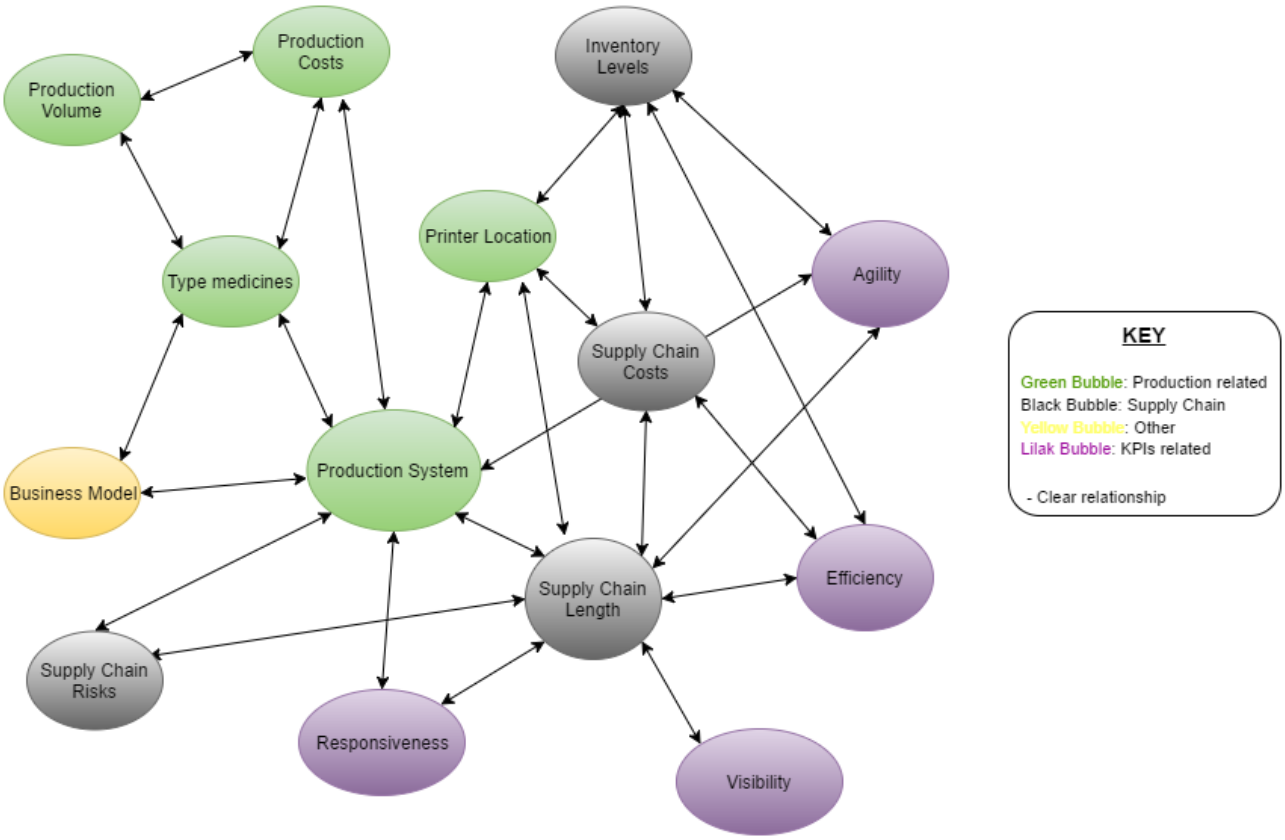

Figure 27 Experts key words. Source: this project

The issue map in figure 27 serves as a model validation technique too because most of the relationships are the expected when considering this key terms connections. Also, it helps to realize which the core terms are: the **production system** determines which **type of medicines** can be produced, the **business model** that the company would pursue, the **location of the printer** and all those establish the **production costs**. These core terms will be included afterwards in the supply chain re-design inputs in table 6 and 7 (section 5.3). For example, the type of medicines and printer location are considered as design constraints because the design itself depends on what type of medicine is produced and where the printer is located. On the other hand, **inventory levels, SC costs, SC length and SC risks** are categorized under supply chain

metrics that would be used to measure each alternative supply chain performance. Besides, the categories that the key words are organized into (supply chain terms, production related, performance or KPI terms and others (mainly business terms)), are the ones to be used to organize the design terms as well. Nevertheless, the categories will be further developed with some more information from literature and researcher's own opinion.

The interconnections are bidirectional because at the time that the production system establishes which type of medicines could be produced, the same happens at the opposite direction: the type of medicines produced would require a production system more centralized or decentralized and that would affect the printers' position. Besides, a part from being bidirectional, the connections are due to influences. As already explained, the type of medicine determines the production system, etc. The power of each connection was not established, so a part from determining which are the key or core elements, the power of their influence towards the other factors was not demonstrated.

From the issue maps in figures 23-26, the first ideas of the key design requirements and 3D printing opportunities can be already pointed. The first key finding regarding drug 3D printing is the **non-agreement** between experts regarding **production volume** and the **technical requirements.** Each group of actors that had the expertise to answer the production volume question responded in a different way: some pointed that the volume will depend on the scale and location of the printer, others point at producing small volumes of customized medicines and the others that the volume will depend on the clinical need for this type of medicines. And regarding the **technical requirements**, the majority **agreed** on the need of new materials, but a part from this, each of the actors pointed to different other needs: packing systems, cleaning and digital tread (data storage and analysis systems). The most surprising fact was the **clearly disagreement** regarding the need of faster printers. While some pointed towards this as an essential need to enable drug 3D printing, other experts claimed that the current printers are enough to serve the initial markets for 3D printed personalized medicine. Maybe in the long term printers with higher speed are required but with the capacity to print 1 pill per minute, those experts were more than confident that drug 3D printing in any location would be possible.

Another essential finding is that while some experts found topics important to solve before considering drug 3D printing a reality, others already had the answers to them. For example, **dosing accuracy** which some experts pointed their concerns surrounding this topic while others commented that the current printers enable a perfect accuracy in dosage even for low concentrations. Regarding **expiration date**, most likely it will be established by carrying stability studies. However, regulatory experts pointed that most probably it would be very similar to current expiration dates of solid dosage forms. In the pharmaceutical field, expiration is a major consideration when determining inventory days and inventory storage. Product expiration is a major cause of financial losses and lack of stock somewhere else (Privett, & Gonsalvez, 2014).

Topics that after the literature review seemed important concerns regarding regulation such as drug **counterfeiting** and **traceability**, after asking the experts, they were no longer concern matters. For counterfeiting, first of all, if the drugs are personalized and produced in small amounts, there's not much gain in producing fake copies of them. But if drug 3D printing became a mass production, then barcodes

could be printed on the tablets to avoid fake drugs arrive to the market and as a key indicator for patients to detect regulated drugs. Similar to barcodes, it would also be possible to print company's trade mark on the drug to prove its authenticity. Furthermore, traceability is not a problem because all the production and delivery system is shorter and digitally controlled.

5.2.2. 3D printer positioning in the supply chain

First of all, before positioning 3D printing production system in the supply chain, it is essential to define what the product would be. This is due to the fact that for the customer to get a personalized pill, its production would require more than just the 3D printer. In order to produce a personalized drug by 3D printing, it would be required at least one diagnostic test, an algorithm to guide the use of the drug or the diagnostic-drug combination and the drug produced by 3D printing (Miller, 2013). Apart from vast clinical trials to ensure drug's safety. After defining the diagnostic tests necessary to develop the personalized medicines, where could the 3D printer be located?

Many possibilities do exist of where to locate the 3D printing machine. One could be that the **pharmacists tailor and print out customized drugs on demand** so they will suffer a change in their role in the upcoming years. They would have reels of filaments of the base product (API plus solvent) and customize the dose and the shape of the tablet to the customer's individual needs (Robinson, 2015). If most common medications become available by this system, patients might be able to reduce their pill burden[2] to one polypill per day (Ventola, 2014). However, polypills can be a reality in terms of technological means but to be accepted by regulators, that's a long term possibility.

Another possibility would be that **pharmacists add the amount of a given API to a previously manufactured excipient or directly define which API do the customer need** and manufacture the whole pill. This alternative is more complicated because it needs a diagnostic side. Thus, it could either be than the patient gets their blood tested in the hospital where a doctor determines the dosage and the API required and that information is sent to the pharmacists, who will print the medicine. Or it could be that the blood test and the printing are done directly at the pharmacy. Another possibility is that **3D printers will be placed in a couple of factories**, where they will print on-demand and send directly to customers' home. This alternative wouldn't produce many changes from current practice (Meyer, 2015). Another possibility is that **doctors can custom pill's dosage** directly at the hospital (Reads, 2015) (see figure 28).

[2] *Pill burden* refers to the number of pills a patient takes per day.

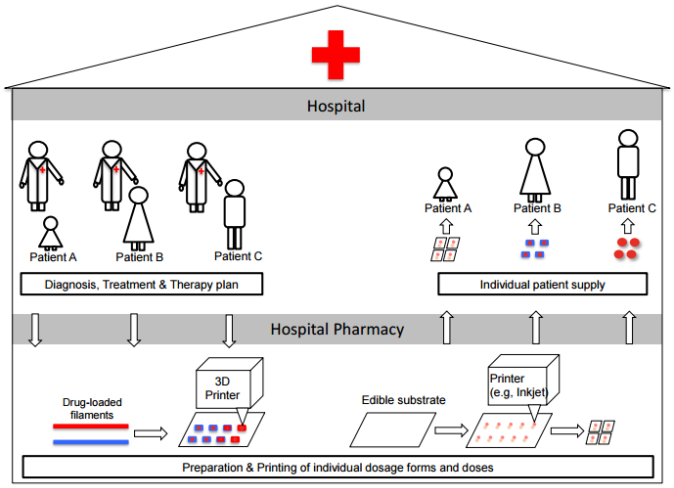

Figure 28 Drug 3D printing procedure in hospitals. Source: (Sandler, 2015).

Dr. Lee Cronin, who has created a method to obtain 3D printed drugs called "chemputer", claims that by using this new treatment method, the whole pharmaceutical industry could change: consumers would be entitled with all the control over production. His idea is that prescription patients would buy a chemical "ink" and a "blueprint" at an online pharmacy, and then **print the medicine at home** with a 3D printer and the required software(Le, 2013). Therefore, it will be a moment when 3D printers could be present at all homes like microwaves. From a consumer perspective, at least printers, material and blue prints standardization will be required.

However, not everyone is as optimistic as Dr. Cronin. In a report published in by the consultancy Deloitte, 3D printing will be a revolution for the market but not for the customer. This means that even the unit prize of 3D printers will be expensive, they are difficult to calibrate, maintain and they would require many ingredients. Furthermore, production by 3D printing makes a substantial difference when there's no room for machines, parts suppliers are located very far from the production and assembly or when the components are better produced by 3D printing (for example because their complexity) (Predictions 2015: 3D printing is a revolution, 2015). But the possibility of printing almost any object with any type of material is not yet possible. For this reason, according to Deloitte's report, 3D printers won't be ubiquitous like laptops, at least in the near future.

5.2.3. 3D printing drugs benefits

In table 5, the key benefits of personalized drug manufacturing by 3D printing are organized in two main categories: customer experience and supply chain effects.

According to the first group, the key points are a **high probability of a drug's desired effect**, **low probability of side effects** and targeted therapies and **preventive strategies** instead of just reactive medicine (summarizing the findings in section 3.5 Personalized medicine Opportunities).

The supply chain of pharmaceutical companies could suffer many transformations due to the switch of production from mass manufacture to customized 3D printed drugs. The main modifications are: reduced or **eliminated assembly lines and shorter supply chains** for many products depending on the position of

production step. Instead of products, **digital files** containing the designs of the products would **move around** the world and they would be printed anywhere by any printer that meet the design constraints. Furthermore, products could be **make-to-order** (printed on demand) without the need to have extensive inventories of both new products and spare parts. Thus, 3D printing will change the aftermarket service completely and **large regional warehouses could be replaced** by small facilities with on-site 3D printing production. Another possibility is that a manufacturing facility could print a huge range of types of products without retooling and each of them could be customized later on in pharmacies or at customers' home without additional cost (Campbell et al., 2011; Cohen, et al., 2014).

A broader impact could be to **de-globalize production** as it is brought closer to the consumer. This would imply that manufacturing could be pulled back to the countries where the products are consumed, reducing carbon footprint of manufacturing and transport. Thus, 3D printing could help establishing a **cost effective, leaner, faster and efficient supply chain** and spur the formation of a circular economy. Furthermore, current and future leaders in additive manufacture technology could experience a boost in innovation enhancing their geopolitical influence and economic strength (Campbell et al., 2011; Tata Consultancy Services, 2015; Cohen et al., 2014).

Hospitals and pharmacies could manufacture prescriptions on their own premises, eliminating the need to stock vast quantities of products. They would also be able to produce specialized or uncommon compounds in-house, saving patients a considerable wait, and perhaps saving more lives in time-sensitive critical situations. With such flexibility and scalability afforded to supply chains, both suppliers and consumers can benefit from the low costs and prices that operational efficiencies bring(Yeung, 2016).

Besides, 3D printing technologies is not bound by economies of scale as it **doesn't require extensive manufacturing infrastructure**. Not being bounded by economies of scale implies that the cost of producing one unit or one hundred is the same. It can lead to a situation in which the cost of producing custom drugs may be the same or lesser than fabricating thousands using current manufacturing techniques (Tata Consultancy Services, 2015). However, some researchers don't agree with the past statement and strongly believe that additive manufacturing can be under economies of scale terms (see Appendix Part B, supply chain interview transcripts, interview to Dr.X).

To sum up, the supply chain related terms include **traceability** of products (it is an actual trend and challenge that supply chains need to come up with solutions for it), **supply chain length and costs, inventory levels, supply chain risks** and **delivery reliability** (deliveries without errors in time, price, place, quality or quantity). Finally, in terms of KPIs increase in responsiveness, agility, efficiency and visibility.

Table 5. Key benefits of drug production by 3D printing. Source: this project

CATEGORIES	KEY WORDS	SOURCES
Customer experience	Drug desired effect	Ginsburg, G. S., & McCarthy, J. J., 2001; Pennic, 2014.
	Non side effects	
	Preventive therapies	
	Product traceability	Interview: SC & Regulatory experts & literature (University of Sussex, n.d)

Supply chain related	Supply chain length	Interview: SC experts & Literature (University of Sussex., n.d.; "Second Redistributed Manufacturing Healthcare Research Network (RiHN) workshop," 2015; Phillips, W., 2016)
	Inventory levels	Interview: SC experts &Literature (Campbell et al., 2011; Cohen, et al., 2014)
	Supply chain risks	Interview: SC experts & Literature (University of Sussex., n.d.; "Second Redistributed Manufacturing Healthcare Research Network (RiHN) workshop," 2015; Phillips, W., 2016)
	Delivery Reliability	Interview SC experts
KPIs	Responsiveness	Interview: SC experts & Literature (Campbell et al., 2011; Tata Consultancy Services, 2015; Cohen et al., 2014)
	Agility / Flexibility	Interview: SC experts & Literature (Campbell et al., 2011; Tata Consultancy Services, 2015; Cohen et al., 2014)
	Efficiency	Interview: SC experts & Literature (Campbell et al., 2011; Tata Consultancy Services, 2015; Cohen et al., 2014)
	Visibility	Interview: SC experts & Literature under SC trends and challenges (Keskin, 2015; Longman, 2015)

5.2.4. Business strategy

The **market opportunity** in the case of drug 3D printing is to cover an existing need with a new production system. The experts agreed upon that 3D printed personalized medicine would most likely become another **business branch** or segment inside the current pharmaceutical landscape. This strategy would enable the companies to capture the value of this new production system at the same time that they will neither introduce big risks moving towards a completely new production system nor lose the investments in the current system (mainly infrastructure). Some experts put more emphasis on the risk/uncertainty involving a new production system than the sunk costs. That doesn't mean that the costs are not important, but as the pharmaceutical sector has big per unit revenues, they are not so sensible referring to investments and innovation. If they are reluctant or less willing to those big changes is more because of the risks and uncertainty that surrounds them. Most likely the market leaders will be considering all the opportunities that 3D printing can offer to their business. However, until some start-ups or smaller players enter into the commercialization of these new drugs, the experts don't think that they will risk their business to start moving towards this new production method. Therefore, market leaders are more adopting a wait and see strategy. In the long-term, these leaders will probably buyout those small companies or enter in collaborations with them. To sum up, the company's strategy would be to maintain the current production systems and develop a new business branch that will produce personalized drugs by 3D printing or/and by other production methods. By this strategy, the companies will be able to maintain their **high monopolistic profits.**

And last but not least, as already implied in the last paragraph, 3D printing production could enhance the **market entry of new players** due to lower sunk costs (small start-ups). For instance, additive manufacturing reduces the costs to begin manufacturing or to serve niche segments. Furthermore, many

businesses are appearing which offer highly customized designed products for their customers gaining knowledge regarding their tastes and building relationships. Established companies would have difficulties to match. In the beginning, these players will be operating in niche markets were customers will be willing to pay a premium (drugs targeting cancer for example); however, on the long term, they could transform how the value chain is distributed (Cohen, Sargeant, & Somers, 2014). Also, this new market segment has unexpected high profits as many unexploited niches do exist. **Competition** will increase due to all small companies entering the market.

The benefits of 3D printing are tangible; large pharmaceutical companies need to find which the best strategy is: to acquire or invest in these new 3D printing start-ups, partnering with other established companies or developing biologic ink and blueprints (Reads, 2016).

5.3. Supply Chain Re-Design

In this section, the design process described in section 2.2 is applied to come up with a detailed design of the pharmaceutical supply chain where 3D printing is used as a production method. Figure 29 shows a summary of the design process.

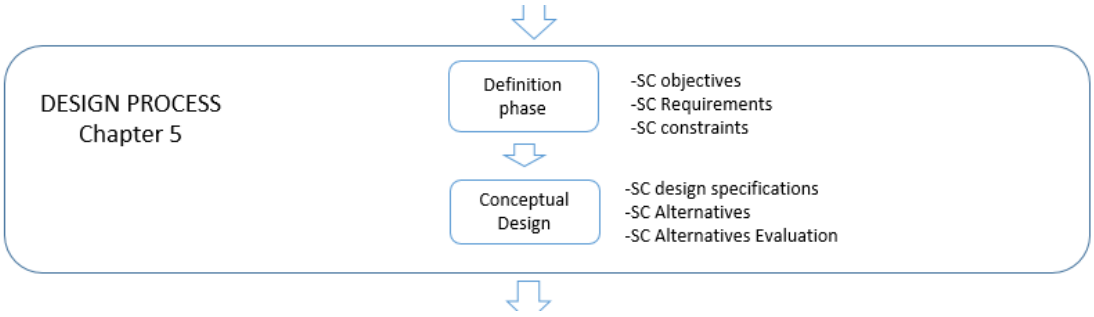

Figure 29 Steps of the design process shown in chapter 5. Source: this project.

Table 6 shows each of the main categories and subcategories obtained in the problem exploration part and then classified into objectives, requirements, constraints, design specifications, design alternatives analysis and after weighting each of them, the overall score. Each X in the table means that the given sub category belongs to that group. By using this classification, a clear idea of the key design requirements, constraints and specifications that will be used in the pharmaceutical supply chain re-design is generated. Finally, table 7 shows the sources of each category, mainly literature review and experts' interviews; however, the researcher's opinion is also included as a reflection on the previous information (it is only specified when it was essential to include that category in the list).

First of all, the **design objectives'** function is to establish what the design wants to accomplish; the **requirements** include all those subcategories that in literature and during the interviews have been pointed as essential to produce drugs by 3D printing. The **design specifications** establish the concepts that can be used to meet the objectives. And the **design constraints** reduce the alternative possibilities as the designs are restricted to certain possibilities. After that, the alternative designs are depictured and the categories scored in the **design alternative analysis** are the ones that enable the analysis of each

alternative. The **sources** for each category are specified in table 7. Each of the following subsections will explain in more detail the previous classification.

Table 6. Supply Chain design inputs specified in an evaluation matrix. Source: this project.

Categories	Subcategories	Objectives	Requirements	Design Specifications	Design Constraints	Design Alternatives Analysis
Production process	Medicine type	X			X	
	Printer Location	X	X	X	X	X
	Production system (centralized or de centralized)		X	X		X
Technical aspects	Cleaning		X			
	Cross-contamination		X			
Regulatory Approval	Safety		X			
	Quality		X			
	Validity		X			
	GMP/Standards		X			
	Stability		X			
	Liability		X			
Business related	Market opportunity	X				
	Business Model					
	Market entry (dynamics)					
	SC position				X	
Supply chain related	Product traceability					X
	SC length					X
	Inventory levels					X
	SC risks					X
	Deliver reliability					X
KPIs	Responsiveness					X
	Agility					X
	Costs					X
	Efficiency					X
	Visibility					X

Table 7. Supply Chain design inputs specified (II). Source: this project

Categories	Subcategories	Sources
Production process	Medicine type	Interviews to all experts (see appendix).
	Printer Location	Interviews & literature (Reads, 2016; Meyer, 2015; Robinson, 2015; Deloitte, 2015) plus researcher's opinion.
	Production system (centralized or de centralized)	Interviews & literature (Jonathan, & Karim, 2016; University of Sussex., n.d.; Second Redistributed Manufacturing Healthcare Research Network (RiHN) workshop, 2015; Phillips, 2016).
Technical aspects	Cleaning	Interview Regulatory experts & literature (Shang, W., 2016; Davies, et al. 2014).
	Cross-contamination	Interview Regulatory experts.

Regulatory Approval	Safety	Interview: Pharma & Regulatory experts & literature (Lesko, 2007; Schork, 2015).
	Quality	Interview: SC & Regulatory experts.
	Validity	Interview: Regulatory & 3DP experts.
	GMP/Standards	Interviews: Regulatory, 3DP & SC experts & literature (Crawford, 2015; Ginsburg, & Willard, 2009; Padilla & Kulkarni, 2014).
	Stability	Interview: 3DP experts.
	Liability	Interview: SC & 3DP experts & literature (Robinson, 2015).
Business related	Market opportunity	Interview: Pharma experts & researcher's opinion.
	Business Model	Interviews: 3DP, Pharma &SC experts.
	Market entry (dynamics)	Interview: Pharma & SC experts & literature (Cohen, Sargeant, & Somers, 2014).
	SC position	Researcher's opinion.
Supply chain related	Product traceability	Interview: SC & Regulatory experts & literature (University of Sussex, n.d).
	SC length	Interview: SC experts & Literature (University of Sussex., n.d.; Second Redistributed Manufacturing Healthcare Research Network (RiHN) workshop, 2015; Phillips, 2016).
	Inventory levels	Interview: SC experts &Literature (Campbell et al., 2011; Cohen, et al., 2014).
	SC risks	Interview: SC experts & Literature (University of Sussex., n.d.; Second Redistributed Manufacturing Healthcare Research Network (RiHN) workshop, 2015; Phillips, 2016).
	Deliver reliability	Interview: SC experts.
KPIs	Responsiveness	Interview: SC experts & Literature (Campbell et al., 2011; Tata Consultancy Services, 2015; Cohen et al., 2014).
	Agility	Interview: SC experts & Literature (Campbell et al., 2011; Tata Consultancy Services, 2015; Cohen et al., 2014).
	Costs	Interview: SC & Regulatory experts & literature (Yeung, 2016).
	Efficiency	Interview: SC experts & Literature (Campbell et al., 2011; Tata Consultancy Services, 2015; Cohen et al., 2014).
	Visibility	Interview: SC experts & Literature under SC trends and challenges (Keskin, 2015; Longman, 2015).

5.3.1. Problem definition

The problem definition is considered the first step of the design process. It consists in developing a better understanding of what is required in order to start looking for solutions of how to provide it.

The main **objective** of the design is to show how the actual pharmaceutical supply chain will be modified if 3D printing is located at different points of the supply chain and which medicines are produced to represent a market opportunity for the pharmaceutical companies.

After defining the main objective, the requirements and constraints of the design scheme will be determined combining the findings from the semi-structured interviews and the literature review.

Design Constraints

The three design constraints as shown in table 6 and 7 are **the medicine type**, **printer location** and the **Supply Chain location**. The importance of the first two were already explained in the issue map in figure 27. And the supply chain location refers to the geographical location. The supply chain re-designs will focus only in the modifications that the western pharmaceutical supply chain might suffer if drugs were produced by 3D printing (this is explained under the research and design scope in section 2.6).

Requirements to produce personalized medicines by 3D printing

In table 8, the essential decisions regarding drug 3D printing are gathered (it collects just the requirements column form tables 6 and 7). Essential in terms of production, technical challenges and regulatory concerns that both literature and experts pointed as key points to be answered before considering drug 3D printing a mass production process.

Medicine type produced by 3D printing**, printer location** and **production systems** (centralized and de centralized models) are the most commented. **GMP regulation** and **standards** (printers and materials) are mentioned as essential to ensure **quality and safety** of the drugs produced. Even **cleaning and cross contamination** are less commented, they were mentioned by the regulatory experts as necessary to establish how 3D printing will be cleaned after use in case that the same printer prints more than one type of medicine; and for the same reason, how cross contamination would be avoided. Other points of concern are **liability** (who takes responsibility if a drug has side effects because it was not produced correctly or who printed the medicine had mistaken the recipes and printed something else) issues and safety (how can be the pills declared safe and quality proof?).

Table 8. Essential keys for drug 3D printing success. Source: this project

CATEGORIES	SUB CATEGORIES
Production process	Medicine type
	Printer Location
	Production system (centralized or de centralized)
Technical aspects	Cleaning
	Cross-contamination
Regulatory Approval	Safety
	Quality
	Validity
	GMP/Standards
	Stability
	Liability

The **type of medicines** would most likely be personalized medicine that is not possible to be produced with the current system or not effective enough. There are three possibilities: sensors that detect the dosage and the medication timing to ensure correct medication, new medicines completely personalized but with relative high demand (targeting a specific population group) or/and orphan drugs and niche markets. It is essential to point out that, as some experts mentioned in their interviews, 3D printing is

already being seriously considered by pharmaceutical companies as a production method for personalized medicine. The most likely medicines to be 3D printed are sensors that enable personalized treatment when data is gathered and linked with a health problem. These sensors will move medical treatments to become preventive and to fit patients' needs. A likely alternative is a printer with different API filaments that can combine them into tablets with a relative broad spectrum of patients that need the different personalized compositions. And the least likely alternative is a chemputer that synthetizes APIs directly just providing the chemical composition.

The **production system** would most likely be a decentralized model in the long-term where medicines will be printed either in the hospital or in the pharmacy. The experts don't agree upon if medicines would be printed at home (more difficult to ensure quality and safety under regulation perspective). What it is clear is that if that alternative takes place in the end, it would be in a very long-term perspective. **Quality** of the product would be ensured by establishing quality standards by using approved filaments or inks and standard 3D printers. Furthermore, after printing in pharmacies or hospitals, a quality check step could be added to ensure quality.

The main **technical concerns** are cleaning and cross-contamination, both points depend on using the machines for producing more than one drug (multi-purpose machines) or having each machine to produce one drug specifically. Nevertheless, the second option is less likely at least in the long term due to high costs that having a single machine for each personalized drug would imply. It could be possible that in the early stages where few drugs would be personalized, the same printer could produce different medicines or to simplify cleaning and cross contamination problems, different printers will be used. Also, as it has been previously pointed, the pharmaceutical field is highly regulated.

Drug regulation embraces from R&D stages of drug production to commercialization and during products' life. Regulation and standards are required to ensure patients that the drugs that they are buying will have the effect that is said in the box at the same time of controlling the industry's profit margins and their investing activities. For this reason, some key words are categorized as regulatory concerns: **regulatory approval, standards** (some experts have pointed the need to establish standards in terms of machines and materials that ensure process quality and validity), **liability** (if a drug fails to have its effects or have an unexpected one, who would be accounted for that), **quality and safety**. The last two terms are the most important ones regarding FDA medicine approval. As long as the medicine has the necessary quality and safety, the FDA would accept them. Besides, the pharmaceutical regulators interviews disclosed that known GMP rules should apply to drug 3D printing so not much changes would be required; the drug will be regulated and the production method as it is done right now. However, that would also vary between countries: EU and USA don't have specific regulations for solid dosage forms, but China and India have special manufacturing requirements to ensure safety and quality. Another key topic regarding regulation is that until now pharmacists can produce small and personalized volume of medicines, so at the first sight, they could print drugs too. However, would it change with 3D printing in pharmacies? At the first, it should be possible without any regulation change as long as quality and safety are ensured. An option would be to start drug 3D printing at the developing countries as there, pharmaceutical production is more common and accepted. Another point of interest regarding regulation are **polypills**. In the literature review those have been highlighted as a very promising application for drug 3D printing. However,

polypills are highly unlikely to be in the market at least in the short-term. According to regulators interview, that's because it's uncertain how different APIs would interact. Nonetheless, a 3D expert who has widely proven the production of polypills pointed that after **stability** studies that ensure quality and safety, those pills shouldn't represent any challenge. Nevertheless, they would require a change in regulation and more tests because the current rules are applicable to single pills. And here is the resistance that regulators have on this type of pills.

Referring to **liability**, the 3D printer user would most likely be liable assuming that the 3D printer has been tested to ensure GMP standards and that the filaments or chemical inks have been certified before exiting the pharmaceutical company. The doctors or pharmacists are less likely to be liable for the medicines as they are not printing them. Besides the previous challenges, the most essential concern is **process validation**.

The technical and regulatory requirements which belong to the implementation strategy of drug 3D printing are not established by the experts yet. For this reason, they were scoped out in the design process and not defined in the SCOR models. More detailed explanation is provided at the alternative design analysis at the end of section 5.3.2.

5.3.2. Conceptual design

After defining the objectives and establishing the main requirements and constraints, the next step involves stipulating the design specifications and then, generate the alternatives.

Alternative Supply Chain Design specifications

According to the main findings gathered in tables 7 and 8 at the beginning of Supply Chain Re-design sub section, the position of the 3D printer production will govern the different supply chain alternative models. The production system (centralized or de centralized manufacture model) as shown in figure 23, is determined by the manufacture point position.

Depending on the production point is located, all aspects of the supply chain from manufacture to delivery are affected such as supply chain length, costs, inventory levels, agility, efficiency and visibility. Furthermore, in the case of personalized medicine production, is at the manufacturing point where the value for the customer gets to the maximum level. For these two reasons, 3D printing positioning has been established as the main design specification.

Generate Supply chain alternatives

The design specification is the **position of the 3D printer for drug production in the supply chain**. With a pre-analysis at a company level position, there are many points where the manufacturing can be located: manufacturing site, wholesalers, secondary wholesalers, central warehouses, pharmacies and hospitals, new on site manufacturing specialized in 3D printing, each patient's house, etc. Therefore, using the information in section (5.2), the possibilities where to locate the production system are narrowed down to: at the manufacturing site, at hospitals, pharmacies or at each patients' home. Regardless the discussed likelihood according to field experts, all four alternatives will be modelled and further assessed in next sub section.

Each basic supply chain part is depictured as a chain of source (S), make (M) and delivery (D) activities coordinated with planning and returns (R) (Council, 2010; Huan, Sheoran, & Wang, 2004).

A second level of metrics includes the process categories Make-to-Stock, Make-to-Order und Engineer-to-Order which are used to describe the supply chain strategy: stocked product (S1, M1, D1 and D4), Make-to-order (S2, M2, D2) and engineer-to-order (S3, M3, D3). Furthermore, R1 stands for returning expired product, R2 for MRO[3] product (this doesn't apply for the pharmaceutical field as refers to the process of repairing products) and R3 stands for returning excess of product or materials. Finally, the planning processes are divided into: P1 (plan supply chain), P2 (plan source), P3 (plan make), P4 (plan deliver) and P5 (plan return). Planning the supply chain considers its requirements, resources, link them and communicate the supply chain plans throughout all the supply chain. The rest of planning involve the same steps but applied to each activity.

Developing further the scheme presented in chapter 1, a SCOR model of the actual pharmaceutical supply chain is presented in figure 30.

[3] *MRO product* stands for maintenance, repair and operations.

Actual pharmaceutical supply chain

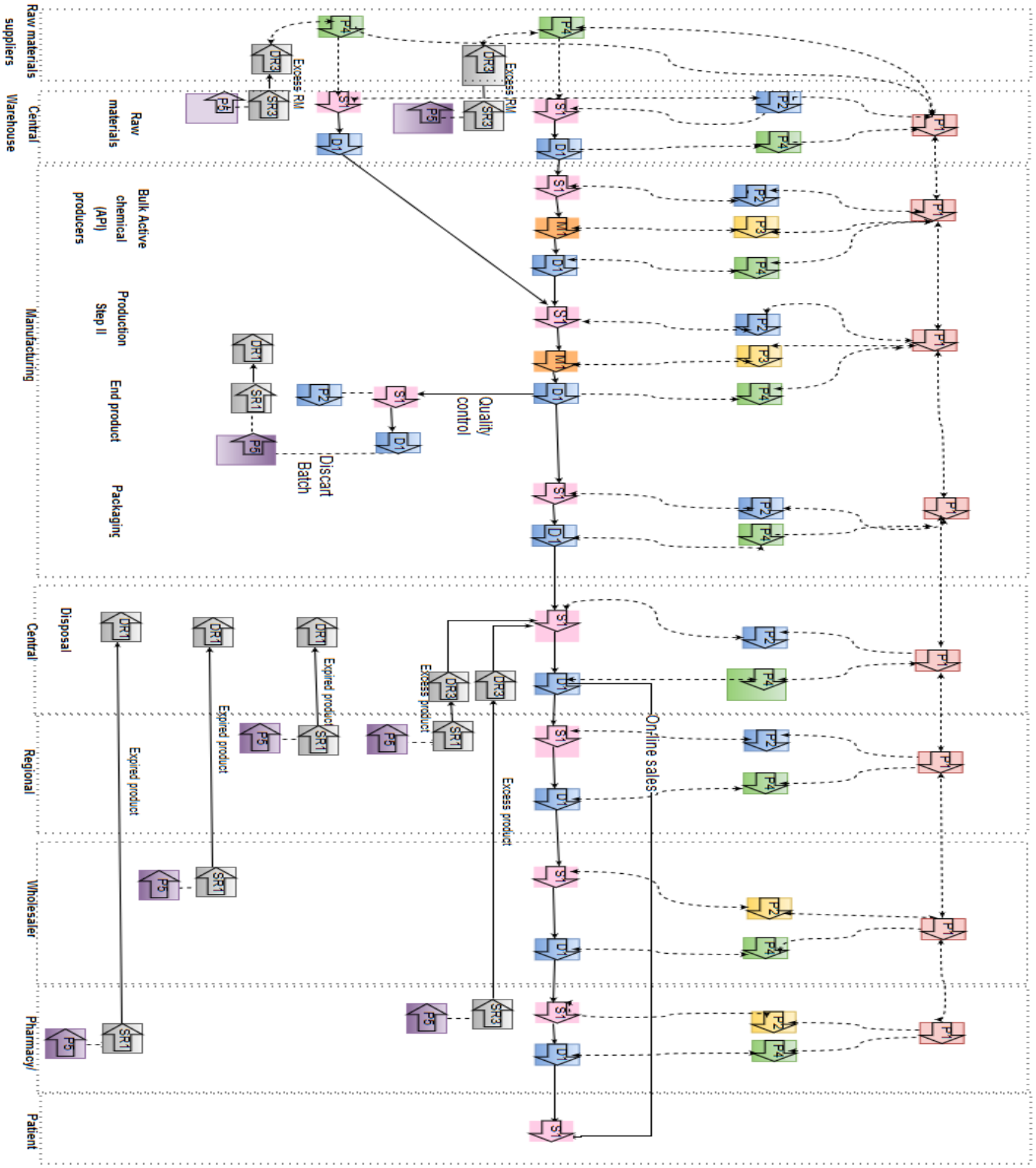

Figure 30 Actual pharmaceutical supply chain modelled with SCOR. Source: this project.

Key: S1 (source to stock, rose), M1 (make to stock, orange), D1 (deliver to stock, blue), P1 (plan supply chain, red), P2 (plan source, blue), P3 (plan make, yellow), P4 (plan deliver, green), P5 (plan return, lilac), SR1 (source return expired product, grey) and DR1 (deliver return expired product, grey), SR3 (source return excess product, grey) and DR3 (deliver return excess product, grey).

The supply chain is divided into **8 stages**: raw materials suppliers, central warehouse, manufacturing facilities, central warehouse, regional warehouse, wholesalers, pharmacies and hospitals and finally, the patient (in the figure a square limit each of the supply chain nodes). The raw material supplier provides to the central warehouse (S1) the quantities that have been agreed upon (P1) and planned accordingly (P4). In order to manufacture the solid oral dosages, an API is required plus some excipients. In the **production step 1** from the raw materials supplied (S1) and stored in the central warehouse (D1), the bulk active chemical is produced (S1, M1, D1). In the **second production step** the bulk active chemical is combined with the excipients directly from the suppliers (S1, M1, and D1 again but in S1 the API delivered after its production (D1) is combined with D1 that comes directly from the central warehouse (excipients)). The excess and expired raw materials are returned from the central warehouse to the suppliers (R3 arrows indicate the excess and R1 the expired). As happens at the other stages of the process, first something needs to be supplied (S) and delivered (D). In this case, to specify that it's a return flow, a R is included at the supply arrow so instead of S it is SR. After the manufacturing phase (the second M at the graph), there's a quality control step in which a sample of the produced batch of pills is taken and analysed and checked against the quality standards. If the batch is approved, it moves to the following step: packaging and then sending the products to the central warehouse (D1 after S1 at packing to S1 at the warehouse) where are kept until an order is issued. As all the procedure is Make-to-stock, all steps are 1; when the production method would be make-to-order (supply chain re-designs 2-4) some of the steps would be 2 instead of 1. However, if the quality test fails, the batch is discarded (R1) and destroyed.

From the central warehouse the order is sent to the regional warehouse (D1 to S1) and from those to the wholesalers (D1 to S1) who either sent them to another wholesaler or to the pharmacy (D1 to S1) and/or to the hospitals (D1 to S1). As no changes are applied to the medicines, all points are S1 (the supplier) to D1 (the receiver). The patient will go to the pharmacy or to the hospital to get the medicine (S1). From the wholesaler and the regional warehouse, the excess (R3) and expired products (R1) are sent a back to the central warehouse where the first ones are stored again whereas the second are destroyed (disposal). The arrows code is the same as previously explained with and added R to the Sourcing. Another distribution channel is the online sales in which the products are distributed from the central warehouse directly to the customers.

Furthermore, each step of the process, so each sourcing (S), Delivery (D), Return (R) and Manufacturing (M) needs a planning step. To plan the supply chain, so connecting sourcing with delivery and manufacture, P1 (it has to be connected with each planning step as the figure shows); to plan source P2, to plan production P3, to plan delivery P4 and return P5. The material flows are depictured with straight lines and the information flow with curved and doted lines.

Some key points of this alternative are the need of both central and regional warehouses and two more nodes from the regional warehouses to the customer (so, from manufacturing to the patient 4 stages are employed). Each node in the supply chain adds more complexity and thus, less flexibility and agility to

adapt the supply chain to the changing needs. Furthermore, the necessity of large inventories in central and regional warehouses leads to high stocked medicines inventory levels. The number of stages and the necessity of huge inventories reduce the supply chain optimization (less lean supply chain); complicating planning activities, reducing the ability to adapt to changes in demand and increasing costs (stocked inventory occupies space without generating profits and has risks to expire).

Depending on the location of the 3D printer, the logistics of the company will differ. According to the previous findings, three different alternatives do exist: the printer is located at the manufacturing site (ALTERNATIVE 1 shown in figure 31), at the hospital (ALTERNATIVE 2 shown in figure 32), at the pharmacy (ALTERNATIVE 3 shown in figure 33) or at each patient's home (ALTERNATIVE 4A and 4B figures 34 and 35 respectively). To simplify things, each alternative only considers 3D printing as the unique manufacturing model. Later on will be further discussed regarding the possibility to combine it with current manufacturing processes. Each design is already validated by the experts instead of showing here the design drafts and include the definitive in the following section.

The key effects on the supply chain/manufacturing system with 3D printing are **eliminating assembly lines**, transform production towards **make-to-order** and **eliminating regional warehouses**; in each case it will be analysed how are those affected**.**

ALTERNATIVE 1 – 3D printer at the manufacturing site

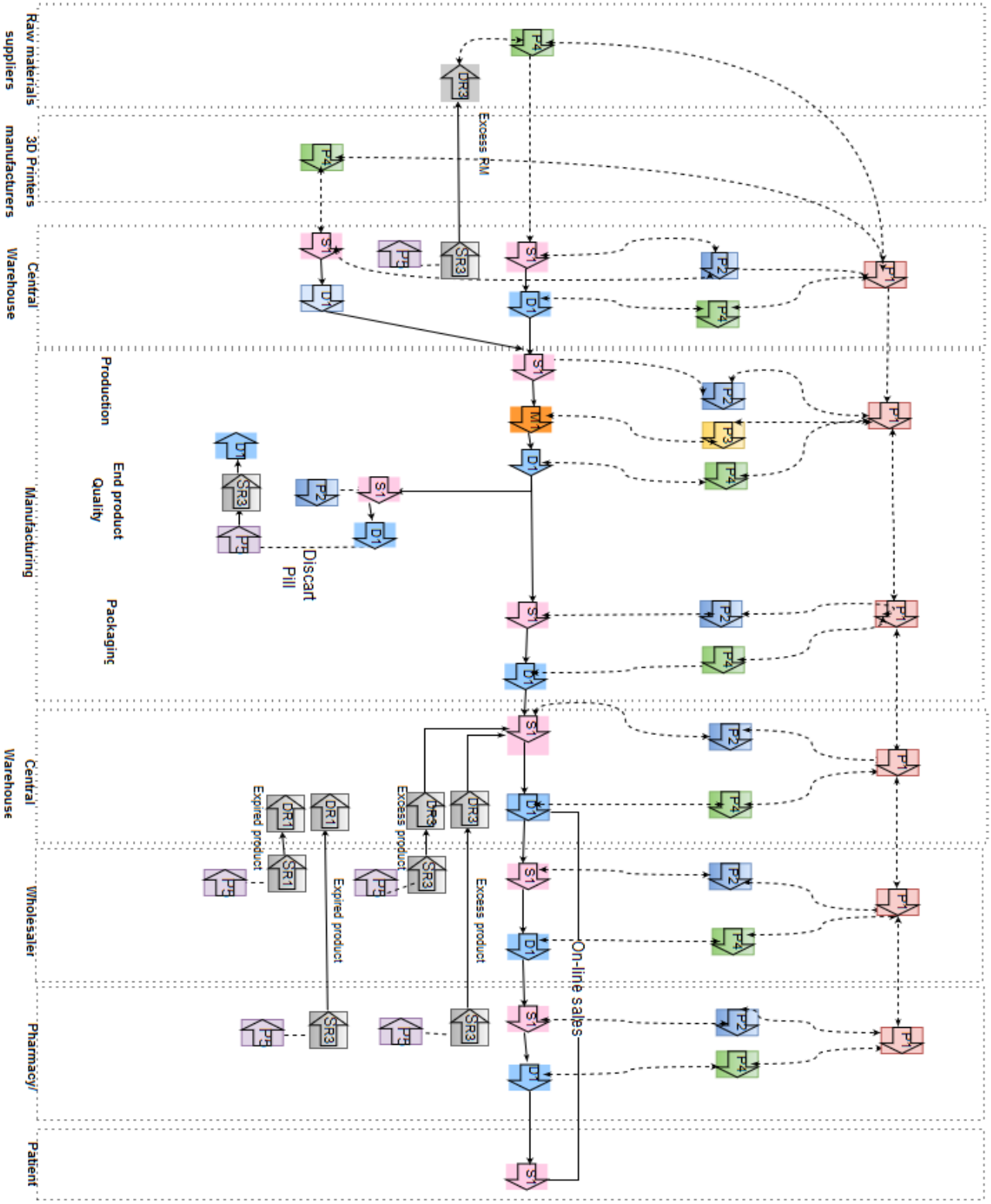

Figure 31 3D printing machine at the manufacturing site modelled with SCOR. Source: this project.

Key: S1 (source to stock, rose), M1 (make to stock, orange), D1 (deliver to stock, blue), P1 (plan supply chain, red), P2 (plan source, blue), P3 (plan make, yellow), P4 (plan deliver, green), P5 (plan return, lilac), SR1 (source return expired product, grey) and DR1 (deliver return expired product, grey), SR3 (source return excess product, grey) and DR3 (deliver return excess product, grey).

Simplification: the model only shows manufacturing of personalized medicine by 3D printing. Further in the thesis would be argued about the strategy that pharmaceutical companies would employ.

Assumption: the strategy is to manufacture the most common personalized medicine for example those diseases that a diagnosis test does exist.

Main characteristics: one less node in the supply chain (regional warehouses no needed because the products are distributed directly to the wholesalers from the central warehouses). Thus, increases supply chain efficiency and agility**. Source stocked product** in the warehouse still because chemical ingredients always have to be storage somewhere; also, 3D printers would be purchased and kept in the central warehouse. Although, some spare 3D printers would be stored in the warehouse, it is assumed that no excess of printers are returned because the company buys the necessary ones. Hard to say if the quantity would be lower than current manufacturing processes and thus, less inventory would be needed. Raw materials would consist in chemical ingredients like in the previous model plus 3D printers. The manufacturing point is reduced to 1 step instead of two sub processes because the assembly happens in one time with 3D printing. However, it is still make-to-stock because as mentioned in the assumption, the production is based in demand estimations as with the current production system. There's still a quality control process; however, it is not clear how would it be. Most probably similar to actually. Both **expired product stream** and **excess product stream** are still needed because the medicine is stocked. It could also be that these streams are not needed if the production volumes are small but this part is not clear yet according to experts.

Overall, the model is similar to the actual supply chain (still centralized manufacturing model) but with one less step in the distribution part and in the manufacturing process (more efficient) and dependence on a new supplier: 3D printer machines. One of the experts who validated the model pointed that the central warehouse should ideally be removed if we consider that *once the drugs are printed, they should be sent right to the distributor/hospital pharmacy based on a* ***pull model*** *(customer order triggers the printing).*

ALTERNATIVE 2 – 3D printer at hospitals

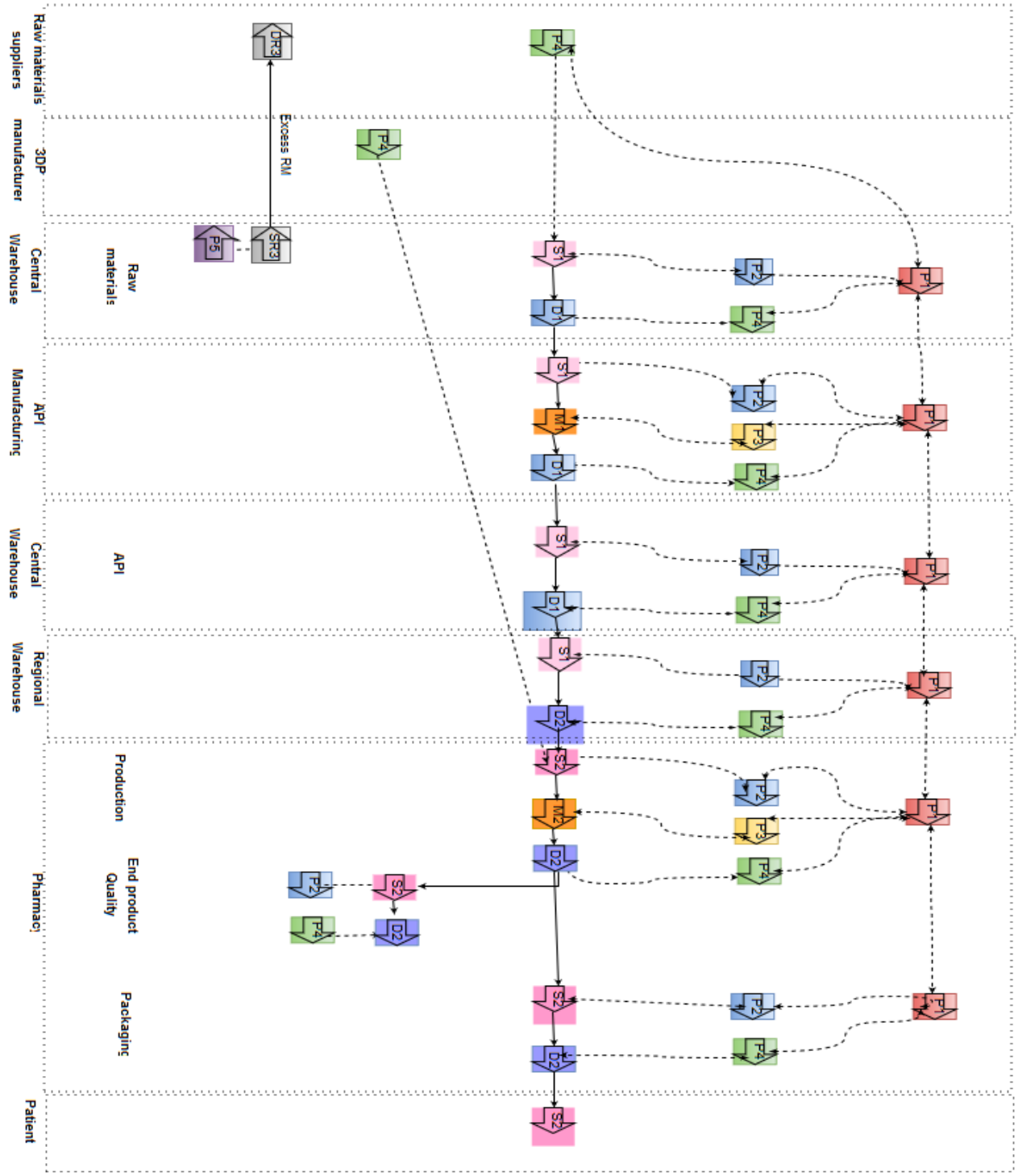

Figure 32 3D Printing machine at the hospital modelled by SCOR. Source: this project.

Key: S1 (source to stock, rose), S2 (source to order, stronger rose), M1 (make to stock, orange), M2 (make to order, stronger orange), D1 (deliver to stock, blue), D2 (deliver to order, stronger blue), P1 (plan supply chain, red), P2 (plan source, blue), P3

(plan make, yellow), P4 (plan deliver, green), P5 (plan return, lilac), SR3 (source return excess product, grey) and DR3 (deliver return excess product, grey).

Main findings: in order to manufacture the medicines at the hospital, the 3D printers are supplied directly from the 3D printer manufacturer but the inks or filaments to produce the medicines (depending on the type of 3D printing machine used) need to be produced at the pharmaceutical manufacturing site. It's highly unlikely that pharmaceutical companies leave the production of the APIs and main components as those represent their highest profits.

The **assumption** is that the printers are directly sold to the hospital. They could be distributed by the pharmaceutical company with the inks/filaments of API but has been pointed as very unlikely. Central warehouse to storage the API. The API volume storage is minimal to supply hospitals so no excess or expired product is returned.

The manufacturing model is still make-to-stock in this stage and the inks/filaments are stored at the central warehouse and sent directly to hospitals. It is assumed that the filaments produced would be the ones with the most common compositions and the same happen with the inks. The actual production of the medicines at the hospital manufacturing centre follows the strategy of **make-to-order**. It could also be that the hospital would have some pills stored as well but to exploit the benefits of 3D printing the strategy, the production's strategy would be to make on demand. In the scheme, there's a point of quality control after manufacturing; however, it is not clear how that would be performed. A packing step is located after quality control but its complexity depends on the production volume; if few pills are produced it might be a manual step but if large volumes are produced, maybe this will require an automatic step. And after packing the medicines are directly distributed to the patient. In this system, regional warehouses and wholesalers are avoided. Furthermore, P1 planning level at the manufacturing point is required, some predictions to calculate the raw materials required for example, but far less than in the actual supply chain. Also, a planning step need to be included at the packing stage in case that it was automatic, if it was manual, most likely the planning level wouldn't be necessary.

This model combines make-to-stock (API manufacturing) and make-to-order (at the hospital production centre). Hence it is used a **decentralized manufacturing model**. As it is produced on demand, no excess or expired product needs to be returned and no inventory is kept (or practically none). Thus, costs are lower and responsiveness and flexibility higher.

ALTERNATIVE 3 – 3D printer at pharmacies

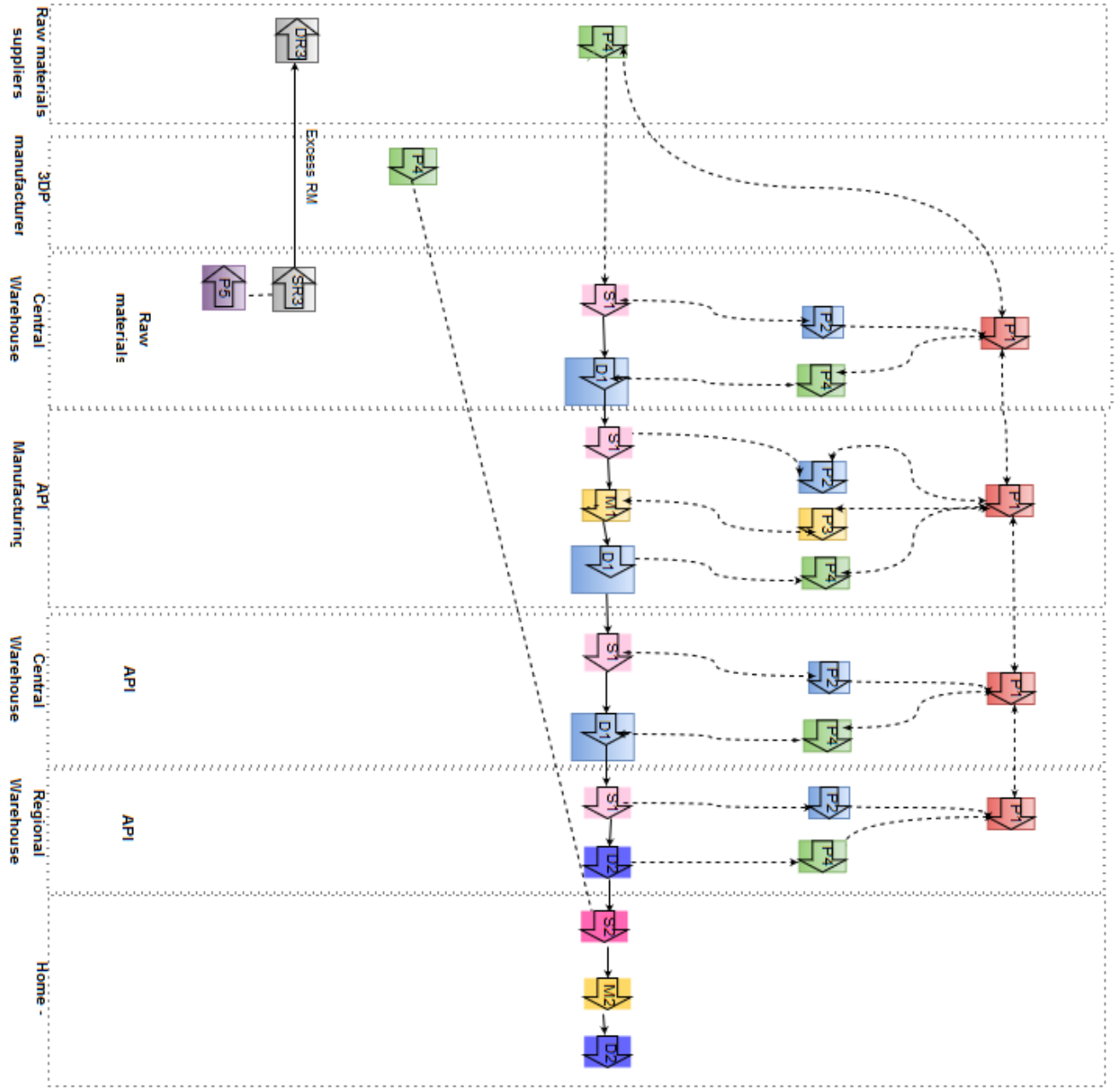

Figure 33 3D Printing at the pharmacy modelled with SCOR. Source: this project.

Key: S1 (source to stock, rose), S2 (source to order, stronger rose), M1 (make to stock, orange), M2 (make to order, stronger orange), D1 (deliver to stock, blue), D2 (deliver to order, stronger blue), P1 (plan supply chain, red), P2 (plan source, blue), P3 (plan make, yellow), P4 (plan deliver, green), P5 (plan return, lilac), SR3 (source return excess product, grey) and DR3 (deliver return excess product, grey).

This alternative is very similar to hospital production but it requires and **extra step at the distribution side** between central warehouses and pharmacies due to smaller distribution volume and more deliveries. And

quality control is added in the model as in the previous alternative but is more unclear how it would be done (it might be manual so no need of this step included in the model) because the production volume would be lower than at the hospital.

ALTERNATIVE 4 – 3D printer at each patient's home

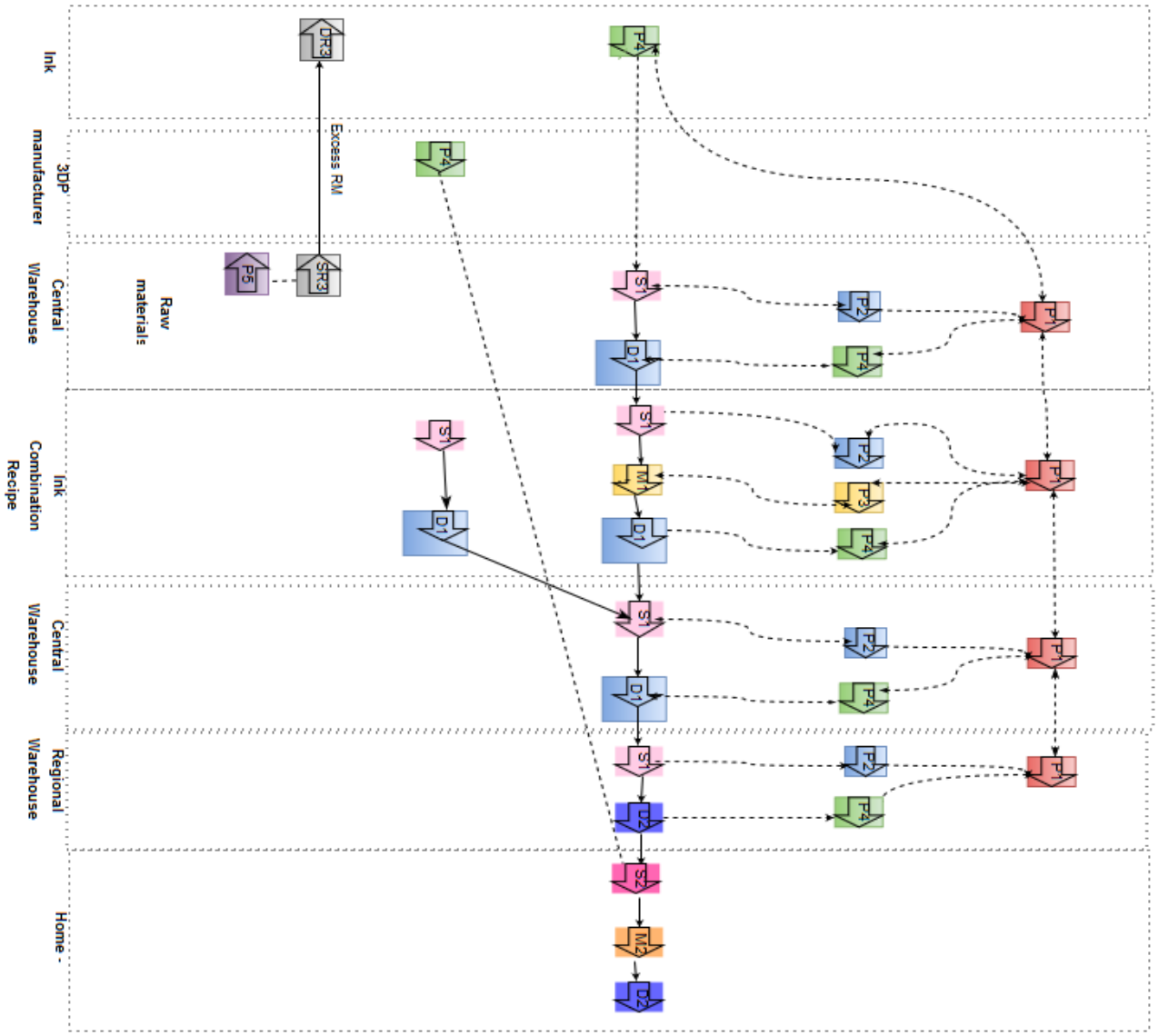

Figure 34 Alternative 4A: 3D printing at each patient's home modelled with SCOR. Source: this project.

Key: S1 (source to stock, rose), S2 (source to order, stronger rose), M1 (make to stock, orange), M2 (make to order, stronger orange), D1 (deliver to stock, blue), D2 (deliver to order, stronger blue), P1 (plan supply chain, red), P2 (plan source, blue), P3 (plan make, yellow), P4 (plan deliver, green), P5 (plan return, lilac), SR3 (source return excess product, grey) and DR3 (deliver return excess product, grey).

Just as the previous models, the raw materials consist in the 3D printing machines plus the inks/ filaments supplied by pharmaceutical companies but this time directly to customers (this model is the same as

current online drug sales). As ALTERNATIVE 3, regional warehouses are needed to supply each customer at least at the national level neither return of excess and/or defective products as they are produced on demand. No planning activities are required because the production happens at users' level at small volumes. It would be interesting to assess then if planning at the regional warehouses would be more complicated. Inventories are reduced to API storage. And production quality control is totally unknown at this point. Also, in the model it's assumed that 3D printer manufacturer could be worldwide or also locally.

Figure 34 shows the alternative where patients could print their own medicines using the current printers. However, as the literature review already pointed, another possibility it to use a chemputer. This is a longer vision of drug 3D printing of more than 20 years from now; however, its implications on the supply chain are analysed in figure 35 as far as they are known until now. The difference between the model shown in figure 34 and this one is that components are home manufactured and synthetized. The main assumption is that only ink is required for the production (no additional ingredients to mix with it). Also, the pharmaceutical companies would source the inks and recipe (certified) obtained from R&D or new department. And the inks would be mixed in the company and then supplied to customers, not more modification. It could also be that the inks are directly bought by a supplier (but this is not shown in the scheme).

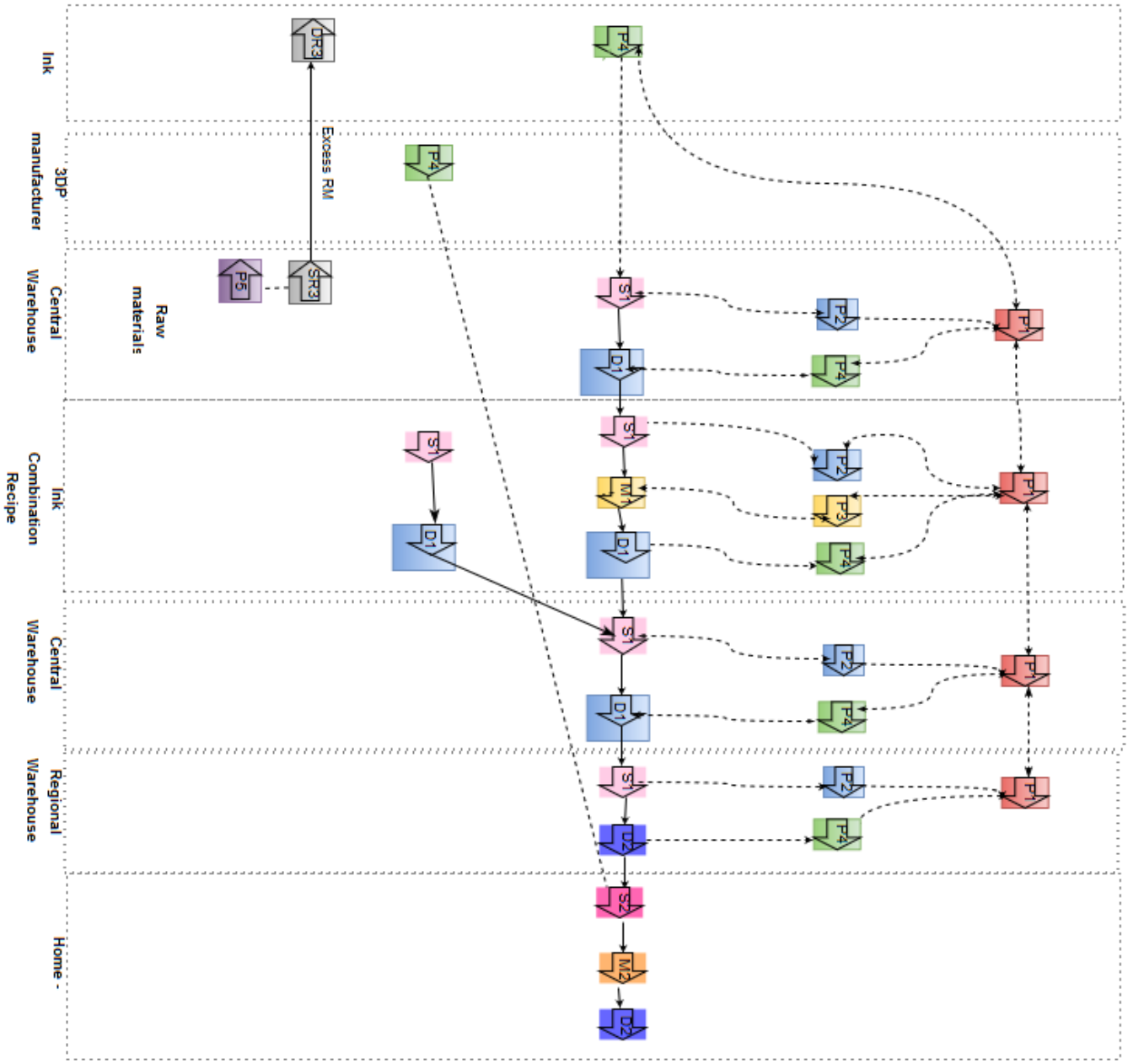

Figure 35 Alternative 4B: 3D printing chemputer at patients' home. Source: this project.

Key: S1 (source to stock, rose), S2 (source to order, stronger rose), M1 (make to stock, yellow), M2 (make to order, stronger orange), D1 (deliver to stock, blue), D2 (deliver to order, stronger blue), P1 (plan supply chain, red), P2 (plan source, blue), P3 (plan make, yellow), P4 (plan deliver, green), P5 (plan return, lilac), SR3 (source return excess product, grey) and DR3 (deliver return excess product, grey).

Supply Chain alternative designs analysis

In this section corresponds the design alternatives will be evaluated. In table 6 and 7 and repeated in table 9, it is pointed that the analysis of the different supply chain alternatives will be done according to how each alternative fulfils each of the Key Performance Indicators and supply chain terms and which production system is used.

Table 9 Supply chain design analysis terms. Source: this project.

Categories	Subcategories
Supply chain related	Product traceability
	SC length
	Inventory levels
	SC risks
	Deliver reliability
KPIs	Responsiveness
	Agility
	Costs
	Efficiency
	Visibility

The analysis of the alternatives was based on the key performance indicators because the other indicators are included in the analysis by assessing their performance: product traceability is implied in supply chain's visibility, supply chain length in supply chain efficiency, visibility and costs; inventory levels in agility, costs and efficiency; and delivery reliability in terms of supply chain responsiveness.

"A performance measure, or a set of performance measures, is used to determine the efficiency and/or effectiveness of an existing system, or to compare competing alternative systems" (Beamon, 1998, p.287). Responsiveness refers to the speed at which tasks are completed, reliability to the ability to achieve a task as projected and agility describes how the supply chain responds to external influences (non-forecasted increases or decreases in demand or natural disasters) and to changes. Costs describes the expenses of operating the process (labour costs, material costs and transportation costs) and asset management attribute refers to the assets utilization efficiency (Ludema, 2015). Supply chain visibility refers to having perfect information of what is happening at each company's process and efficiency is the ability to avoid wasting resources.

In order to evaluate the level of competitiveness of the company´s performance with drug 3D printing, the design alternatives analysis sub categories from table 9 are further developed with information from Beamon, 1998; Min, & Zhou, 2002, see figure 36. Drug 3D printing **flexibility** focuses in adaptation to the demand; **efficiency** focuses on resources utilization, supply chain length and inventory levels. With 3D printing, the production process is triggered by demand pull from customers, thus **responsiveness** is increased: the supply chain can better adapt to demand variance, stock out probability is reduced because the supply does not rely on inventories and delivery reliability is increased as customer needs are directly assessed and fulfilled; **visibility** consists in product traceability (trademarks and barcodes printed on each pill) and supply chain length (visibility increases as the supply chain is closer to the customer because

there are lower steps). **Agility** depends on lower inventory levels (just for raw materials) and lead times in supply chain and production (3D printing eliminates assembly lines and customers are directly served, so lead times mostly disappear). **Costs** are reduced due to shorter supply chains, lower inventory levels and obsolescence of inventory. **Reliability** refers to order fulfilment (meeting customers' needs) and **asset management** to capacity utilization (less inventories and production infrastructure are needed).

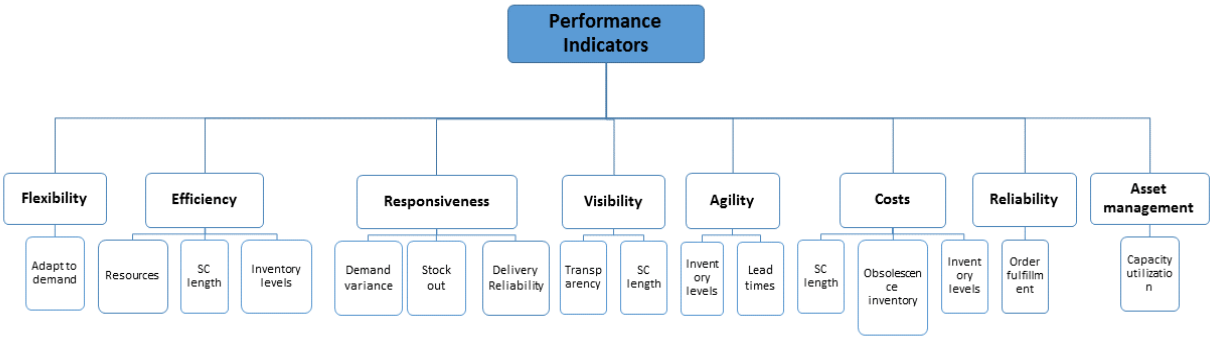

Figure 36 Key Performance Indicators depictured in the fishbone analysis. Source: this project (a more detailed analysis in Appendix Part B performance indicators)

Supply Chain design alternative results

The assumption used to assess each case alternative where 3D printing will be used to produce medicines is how **company´s supply chain performance** is affected. To do so, a qualitative evaluation matrix is applied in which each design outcome, in this case is each supply chain re-design alternative, is checked against the supply chain performance. Each performance indicator is scored according to the impact that 3D printing has on its metrics, the more the impact, the more + are given. For each metric a partial score is provided and then each indicator overall score is used to assess the supply chain's performance. To clarify these results, each alternative is explained separately and the performance indicators scheme shown in figure 36 is coloured according to the results in table 10. The colour key means: white depictures no effect and the more affected a KPI is (the more + the metric has in table 10), the darker the shade of colour blue gets. A more detailed explanation is provided at the key of each scheme.

Table 10 Performance indicators assessed in each case alternative. Source: this project.

Performance indicators	Metrics	ALTERNATIVE 1	ALTERNATIVE 2	ALTERNATIVE 3	ALTERNATIVE 4	ALTERNATIVE 4B
Responsiveness	*Minimize stock out probability*	-	+	++	+++	+++
	Adjust to demand variance	-	+	+	++	+++
	Delivery reliability	-	+	++	+++	+++

	TOTAL RESPONSIVENESS	-	+++	+++++	++++++++	+++++++++
Agility	*Lead times*	+	+	+	++	++
	Inventory levels	-	++	++	+++	+++
	TOTAL AGILITY	+	+++	+++	+++++	+++++
Costs	*SC length*	+	++	+	++	++
	Minimize inventory level (main driven)	-	++	++	+++	+++
	Minimize obsolete inventory (main driven)	-	++	++	+++	+++
	TOTAL COSTS	+	++++++	+++++	+++++++	++++++++
Asset management	*Capacity utilization*	+	+	+	+	+
	TOTAL ASSET M.	+	+	+	+	+
Reliability	*Order fulfilment*	+	++	++	+++	+++
	TOTAL RELIABILITY	+	++	++	+++	+++
Visibility and traceability	*Supply chain transparency*	+	+	++	+++	+++
	SC length	+	++	+	++	++
	TOTAL VISIBILITY	++	+++	+++	+++++	+++++
Flexibility	*Adapt to demand*	-	+	++	+++	++++
	TOTAL FLEXIBILITY	-	+	++	++	+++
Efficiency	*Resource usage*	-	+	+	+	+
	SC length	+	+	+	++	++
	Inventory levels	-	++	++	+++	+++
	TOTAL EFFICIENCY	+	++++	++++	++++++	++++++

From table 10, ALTERNATIVE 1 (**centralized production process**), has equal flexibility because the production system is still make-to-stock and efficiency is higher because of less distribution steps. The model has not increased in responsiveness (speed at which activities are performed); but it has in visibility, agility (less lean times in production), lowered costs (minimized production and distribution costs), asset management increased and reliability due to less steps in the supply chain. The results are depictured in figure 37.

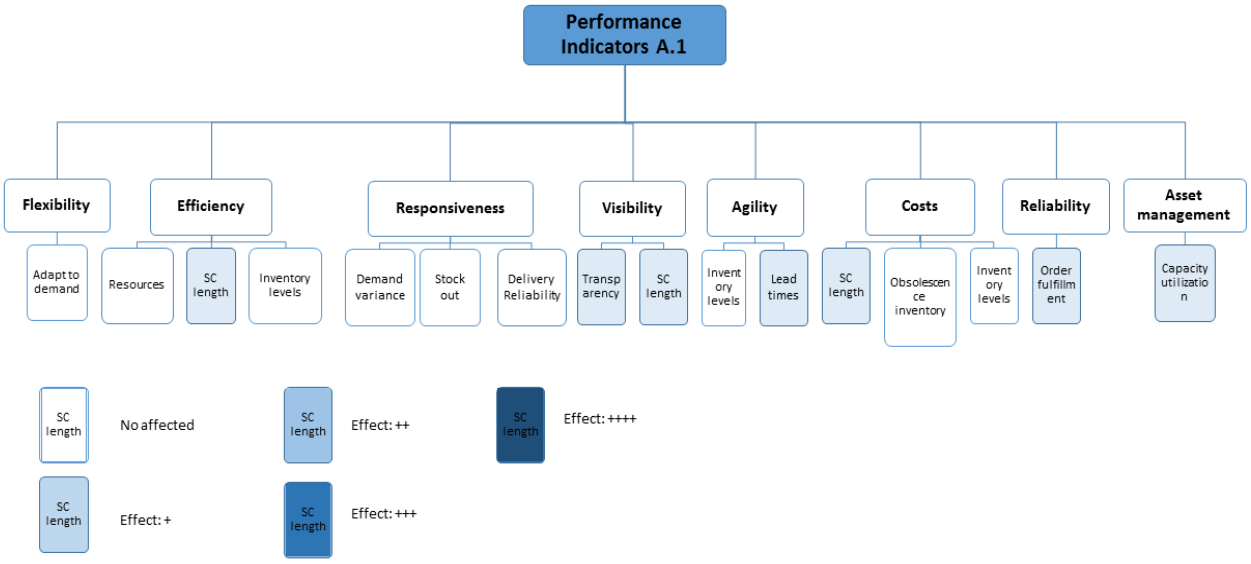

Figure 37 Performance indicators improved by Supply Chain alternative 1. Source: this project

In ALTERNATIVE 2 (**drug 3D production at hospitals**). Flexibility improved but, due to the fact that is a combination of stocked and on demand production, it is not completely efficient (APIs are still stocked in warehouses whereas production of the final drugs is done on demand). Efficiency is higher as overall resources are better used, lower distribution and a business model that exploits an existing need that until now was not covered. Responsiveness is higher because the activities are adjusted to customers' needs (lower stock out probability and more effective to adjust to demand variations). Visibility is better because of less steps in the supply chain and using barcodes on each pill or some kind of trademarks that enables to track each pill individually. Agility is higher because lean times are reduced, no return of products and lower inventory levels. Costs are lower (positive effect) because there are less steps at the supply chain, production method is depending on demand so less raw materials inventory and non from finished products. Asset management improved due to complete use of capacity and greater reliability as the supply chain is closer to customers and fits their needs. The results are depictured in figure 38.

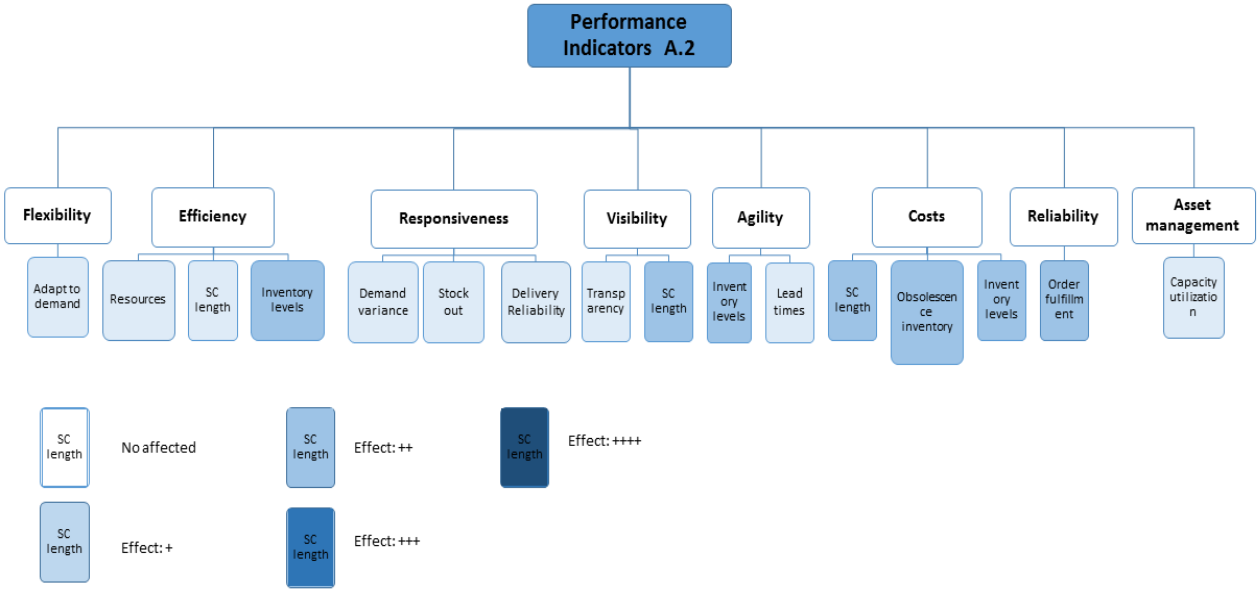

Figure 38 Performance indicators improved by Supply Chain alternative 2. Source: this project

In ALTERNATIVE 3 (**drug 3D production at pharmacies**) responsiveness and flexibility are higher than when producing at hospitals because production is more adjusted to variances in demand and customer needs. Agility is a bit lower due to an extra step (regional warehouses) which also increases the costs and order fulfilment and performance is lower. Visibility is the same as in the previous case and efficiency is lower due to this extra distribution step; although at the same time it is closer to the customer. The results are depictured in figure 39.

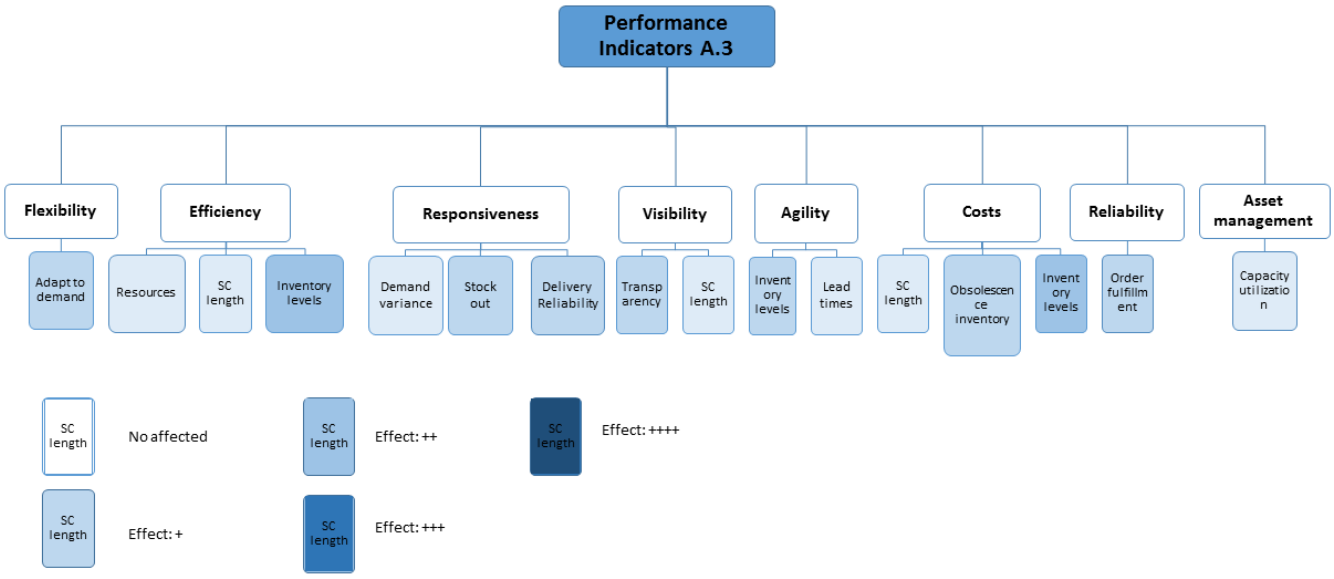

Figure 39 Performance indicators improved by Supply Chain alternative 3. Source: this project

In ALTERNATIVE 4 (drug 3D production at patients' homes) increased responsiveness as production is adjusted to demand and then, less probability of stock outs. Costs are equal to ALTERNATIVE 2, reliability,

visibility, flexibility, agility and efficiency are higher as it is produced directly at patients' home. The results are depictured in figure 40.

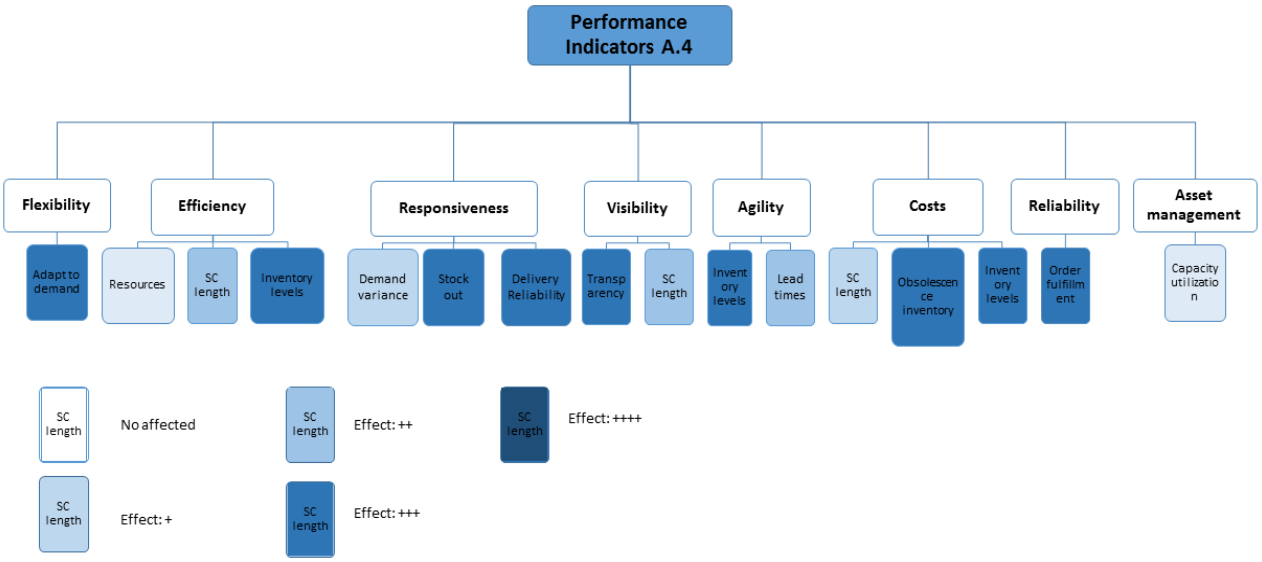

Figure 40 Performance indicators improved by Supply Chain alternative 4. Source: this project

In ALTERNATIVE 4B (drug production at patients' home with a chemputer) the main difference with the previous one are lower manufacturing costs as API manufacture is simplified by just mixing inks. However, due to the fact that the printer can 'in principle' produce any kind of solid dosage form and adjust to demand variance, responsiveness is increased and flexibility as well for the same reason. Efficiency is higher due to lower inventories. The results are depictured in figure 41.

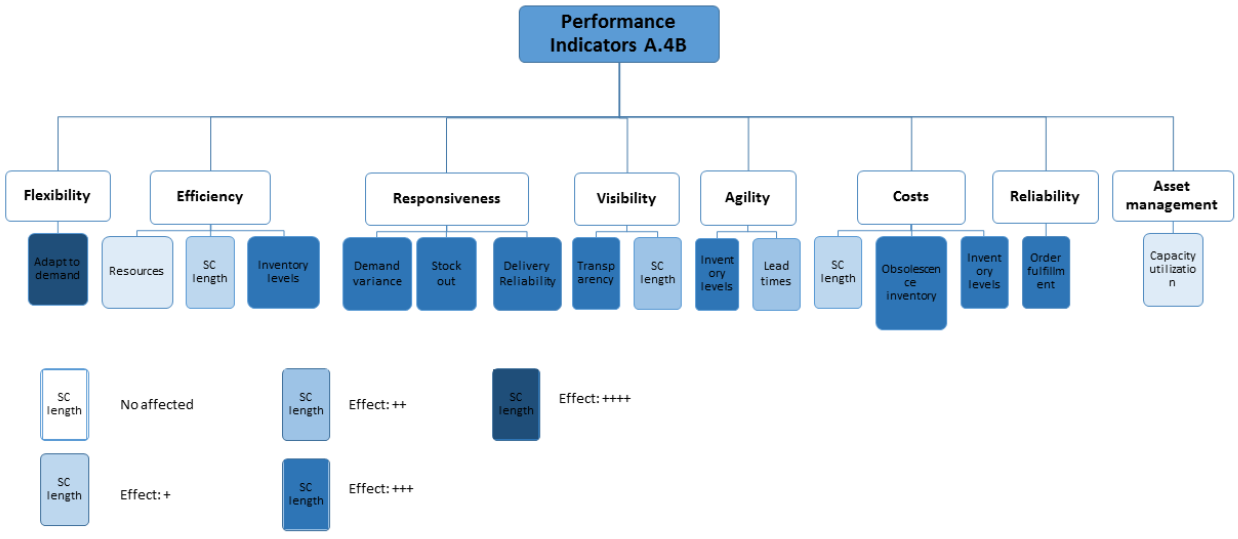

Figure 41 Performance indicators improved by Supply Chain alternative 4B. Source: this project

The reduction of inventory is one of the key benefits when applying 3D printing as a production method. In the different case alternatives inventory obsolesces and stock out probability improved because in the de centralized production systems, products are not stored, only raw materials and API. The differences

between alternatives are due to more storages or less (when the distribution system needs a regional warehouse or not) and if products or raw materials are returned or not.

The **supply chain re-designs** fulfil the **production system** and printer location **requirements** (table 11) and those can be seen in the SCOR models developed. The technical and regulatory requirements are not established yet; as seen in the interviews, the experts are still researching and deciding on them. Thus, in this case, they are treated as extra qualitative requirements which need to be included in a future detailed design and in the implementation strategy. It was mainly due to these non-defined terms that the detailed design was left as future research work.

Table 11. Design requirements. Source: this project.

CATEGORIES	SUB CATEGORIES	Alternative 1	Alternative 2	Alternative 3	Alternative 4	Alternative 4B
Production process	Printer Location	X	X	X	X	X
	Production system (centralized or de centralized)	X	X	X	X	X
Technical aspects	Cleaning	-	-	-	-	-
	Cross-contamination	-	-	-	-	-
Regulatory Approval	Safety	-	-	-	-	-
	Quality	-	-	-	-	-
	Validity	-	-	-	-	-
	GMP/Standards	-	-	-	-	-
	Stability	-	-	-	-	-
	Liability	-	-	-	-	-

And the **design constraints** were medicine type, printer location and Supply Chain location. In all the re-design alternatives these constraints were fulfilled. In all cases, the medicine type is personalized, the location of the manufacture is either centralized or de centralized and the supply chains haven't changed the setting.

5.4. Chapter Conclusions

At the beginning of this chapter, a conceptual model which relates personalized medicine, 3D printing and existing challenges in the pharmaceutical sector is presented. In it is depictured how the tree topics can be related with drug 3D printing. By producing personalized drugs with 3D printing, new medicines can be obtained and tailor-made for each customer's needs. Also, supply chain efficiency could be improved and inventories lowered which are important challenges that the current pharmaceutical field faces. In the following subsection the main impacts of drug 3D printing on the pharmaceutical supply chain are organized. A key finding is that the supply chain performance, the type of medicines and business model depend on the 3D printer positioning.

The next subsection is the supply chain re-design. The re-design process consists in 3 stages: problem definition where the requirements to produce drugs by 3D printing are gathered and explained in detail: liability, safety, cleaning and cross contamination, GMP regulation, medicine type, printer location and production system. Then, the alternative designs are based according to the design specification (3D printer location) and each alternative is evaluated according to the effect on the supply chain's performance. The SCOR model is used to design each of the different case alternatives due to its clarity and convenience. And the last step is design communication which is included in the implementation strategy section (chapter 6 section 4).

The key findings of using 3D printing as a complementary manufacturing system for personalized solid oral dosage forms are: the supply chain becomes shorter and with less transportation volume; thus, becoming more responsible and visible. Also, it's more agile (less lean times), lower inventories at the same time that it becomes more flexible and reliable to fulfil customer needs. And finally, it experiences a cost reduction, not only in the supply chain but also in the production part. Analysing alternative by alternative, **responsiveness** is higher as close the production is to the customer (how supply chain adapts to demand variances, avoid stock outs and delivers the expected product). **Agility** is higher in the decentralized production models, a bit less in the production at the pharmacies as it requires an extra inventory node for the raw materials. In the case of producing at home this fact is shadowed by the increase in agility when the medicine is produced directly at the patient's home. The **costs** are in principle, affected positively, so lowered, in the case where the production takes place at the hospital but the other de centralized manufacturing the costs are low too. However, as experts pointed in the interviews, it is not clear exactly how costs would differ with 3D printing. It is essential to bear in mind that the current production systems are really cost-efficient already. **Reliability** (fulfil customers' needs) and **visibility** are also higher the closest the production is to the customer and the shorter the supply chain is. Finally, the **efficiency** is higher in all de centralized production alternatives.

To sum up, **using 3D printing as a production method in decentralized production systems enhances the company's supply chain performance**. More specifically, the alternative where the printers are positioned at each patients' home is the one where all the indicators are higher. Although, costs are extremely decreased using 3D printing in a de centralized production system, this conclusion is not definitive, needs further research. Besides, with 3D printing, the pharmaceutical supply chain will follow the current trend of increasing visibility and traceability and solve two main challenges: delivery responsiveness and high inventory levels. With a de centralized production model, lower quantity of stocked products and reduced lead times fall into lower forecast dependency, which is a central risk when planning production.

As already mentioned, the business model for drug 3D printing is to **complement the existing business system** but act as a different branch. This represents a big market segment due to orphan drugs, genetic variations, gender and age needs.

The limitations of the design model are first, that a detailed design is not provided due to lack of information and that the analysis method employed is very subjective. The main difficult parameters to assess, both because of the method and the qualitative data, were the differences between alternatives in terms of resources and capacity utilization. Moreover, the key assumption to develop a clearer model

was to just depicture personalized drug production by 3D printing. Thus, in the model were avoided the current manufacture model and other production systems that will provide personalized medicine. The three business branches would most likely coexist but it is also possible that pharmaceutical companies specialize in one branch.

CHAPTER 6. DISCUSSION

In this section, further discussion regarding the drug 3D printing technology itself will be carried to obtain insights on its rate of adoption and some strategies of how to bring it to the market. So, combining this with the supply chain design alternatives provided in chapter 5, obtain a whole picture of drug 3D printing in the pharmaceutical field and suggest an implementation plan for this technology. The topics covered will be technology adoption from one side, and stakeholder analysis and corporate responsibility from the other side. The division helps to understand how the sections are linked. Whereas the technology adoption is an analysis of 3D printing for drugs' adoption phase (how the technology is diffusing); stakeholder analysis considers the power and interest of each group of stakeholders in order to include their opinions in the technological development. At the same time, corporate responsibility aims at adapting the technology to stakeholders' opinions and values to lower rejection and develop them in a responsible way. In the end, everything is combined to provide a plan to implement 3D printing for drugs in the pharmaceutical field. It consists in the short and long term strategies that will provide the required knowledge and solutions to move forward drug 3D printing from its current adoption phase to the market. Figure 42 shows the position that chapter 6 represents in the whole research approach.

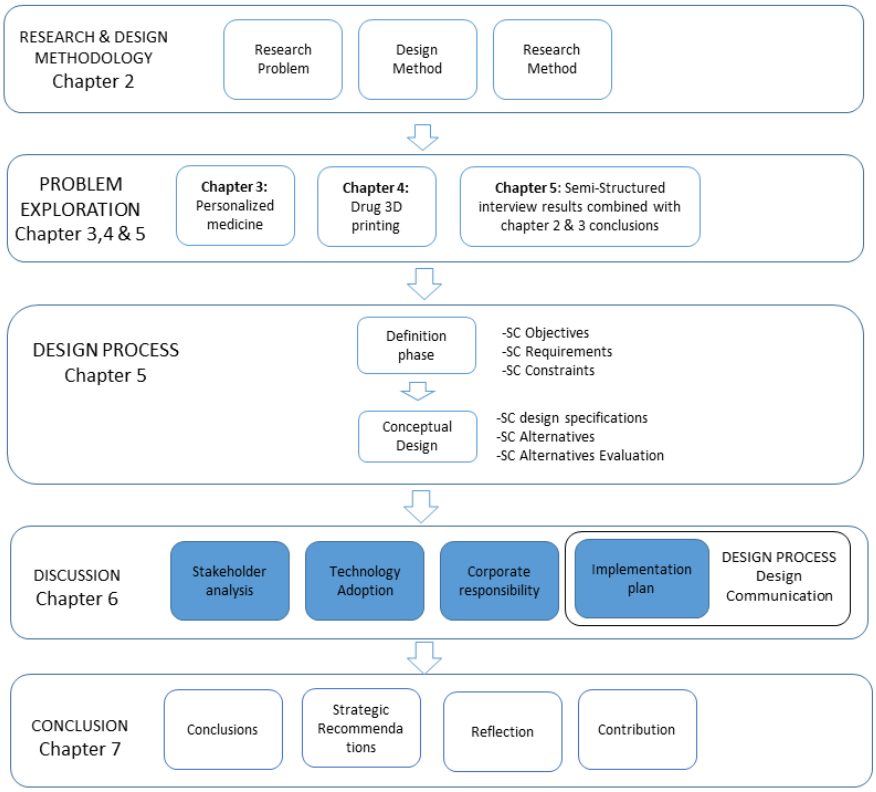

Figure 42 Position of Chapter 6 in the whole research framework. Source: this project

6.1 Technology adoption

A breakthrough technology is considered a technology that has a new type of performance or that follows a new technological principle (Ortt, 2015). According to this definition additive manufacturing is considered as a breakthrough technology.

It's well-thought-out that AM has been introduced by a newly developed technological capability rather than because of a market need (Ortt, 2015). Thus, the introduction of AM into manufacturing is caused by a technology push[4] (Baumers, Dickens, Tuck, & Hague, 2016). The **lack** of either a **market need or a technological substitution** implies less willingness to adopt the technology unless the benefits are clearly showed. On the contrary, personalized medicine is driven by a clinical need so it is market pushed and thus, the adoption is more likely.

Another point to consider is that rarely breakthrough technologies enter the market directly after invention. In fact, the average time from the invention phase to the market depends on the invention and the field; for example, in the case of pharmaceutical products, it takes 10 years due to the required clinical trials and tests. According to Ortt & Schoormans, 2004, the development and diffusion patterns of a breakthrough technology comprises 3 main phases: **innovation, market adaptation and market stabilization phase**. The innovation phase encompasses the period from invention to the first market introduction of a product produced with the given technology. In the case of drug 3D printing it comprises from the invention of 3D printing in the early 1980s to the market introduction of SPRITAM® in 2015. During this phase, the invention is transformed into a commercial product. In the case of 3D printing, the phase comprised the adaptation of the technology to produce chemical compounds and that gave birth to the possibility of producing pills. The reliability and performance of the given technology needs to be increased previous market introduction. After entering in the market, the market adaptation phase starts. The diffusion of the product will be characterized by an erratic pattern of multiple introduction of products in multiple small-scale applications. In the drug 3D printing case, SPRITAM® commercialization started the adaptation phase. However, as pointed previously, the added value that the drug offers represents the infancy of what drug 3D printing can offer. For this reason, drug 3D printing diffusion will require many market introductions and further research to commercialize completely tailor-made 3D printed products.

The techniques required for the production of solid dosage forms already do exist with enough reliability and accuracy. Therefore, the key decisions to be made are **where to locate the 3D printers, ensure quality** (add a step in the production process or a test after production), **safety** and align **regulation** with the production method and location. As the figure 43 already suggests, the market adaptation phase for these products will be up to **10-15 years** from the first market introduction. The length is intuitive, not a definite prospection; it is according the experts opinions on the topic. For this reason, as the technology evolves in an exponential speed, the length can be either reduced to half or doubled. It is during the trials as well were suppliers of complementary products such as printing materials and data analysis tools. A scheme that helps understanding these phases is shown in figure 43.

[4] *Technology push* implies that a technology has been pushed to the market without considering if it satisfies a customer need.

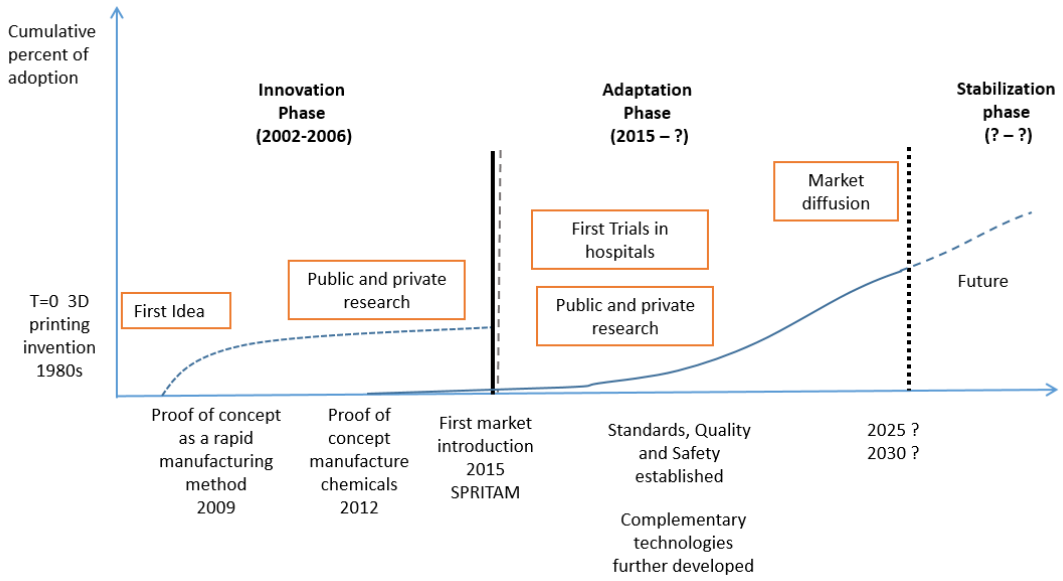

Figure 43 Drug 3D printing adoption phases. Source: this project

The conclusions from this analysis indicate that **commercializing a breakthrough technology is a long process** that can take decades. An implication of this is that small companies may face cash problems and have hard times to survive. On the contrary, large companies are better positioned to survive this period of innovation phase and market adaptation. However, in the case of drug 3D printing, it's been already pointed that although big pharmaceutical companies are researching and developing this technology, is more to assess its opportunities in the market in terms of competitive advantage. This means that pharmaceutical leaders will less likely apply the new technology in production; their strategy is to wait and see what the others are doing until the entrance becomes a strategic viable option. In the pharmaceutical field, given the high risk of not getting the products to the market or failing in the commercialization, being the second in the market has greater advantages and thus, great interest for all the players (**fast follower advantages**). A risk that this strategy has is that other competitors may enter the market first and establish a strong position with high profits and the fast follower struggle to get a share of that market and recap the profits. Nevertheless, during the innovation and market adaptation phase many alliances are required to establish the new market (solve technological challenges and align the technology with the customers' needs).

The high risks combined with great sunk costs linked to the current production system make the environment hard to adopt this new production method (Ortt, 2015; Ortt & Schoormans, 2004; Ortt, Zegveld, & Shah, 2007). Besides, **all the experts are convinced that drug 3D printing represents a huge opportunity to produce personalized medicine and thus, finally be mass produced**.

6.2 Stakeholder analysis

The pharmaceutical industry is composed by a complicated and very sophisticated network of actors which need to be considered when demand and supply are forecasted. The network includes patients (the customers), pharmacies, doctors, payers, the regulation authority (policy makers), logistic companies, insurance businesses, diagnostic corporations and pharmaceutical manufacturers (Wang, 2013).

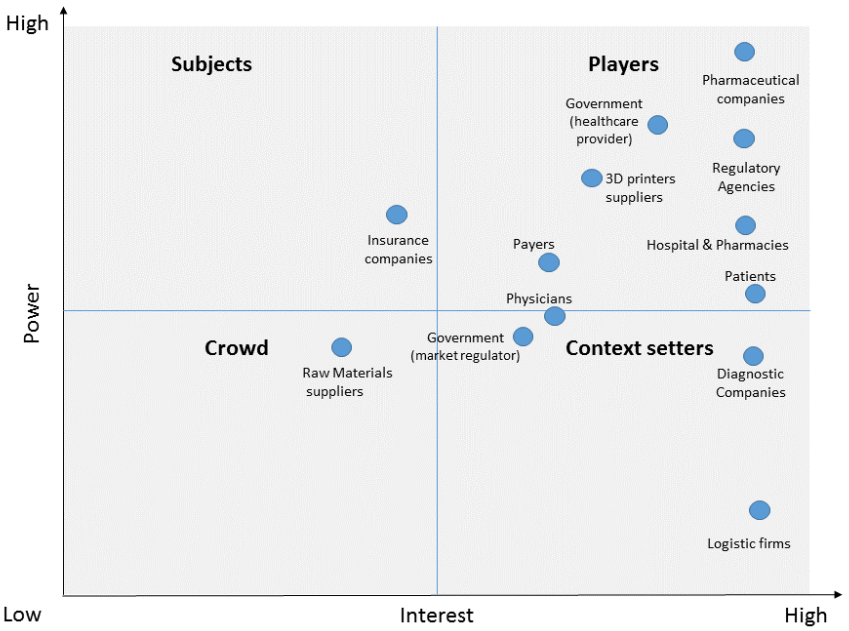

Figure 44 Stakeholders' power versus interest grid. Source: this project.

In the power versus interest grid shown in figure 44, the key stakeholders in drug 3D printing are pointed. The stakeholders' interests against power is plotted, thus providing an overview of the stakeholders whose interests should be taken into account in order to enable drug 3D printing. According to the position at the grid, the stakeholders are organized in four categories: *players* (who have substantial power and interest so, their opinions are of extreme importance), *subjects* (still have high to medium interest but lower power), *context setters* (power but low to non interest) and the *crowd* (stakeholders with little interest and power) (Bryson, 2004).

The key *players* in drug 3D printing are:

Pharmaceutical companies which would sell the blueprints and the base products (inks or filaments) to print the medicines. Nevertheless, the pharmaceutical industry is very conservative. This implies that obtaining the interest from industrial partners could take some time(Sanderson, 2015). Healthcare providers are collaborating and coordinating efforts with payers in order to reduce treatment costs at the same time that greater patient safety and healthcare quality are provided. According to the new supply chain structure envisioned for the following years (2.1 problem definition section), pharmaceutical manufacturers aim to develop **cost effective and high value drugs** with a growing interest towards personalized medicine and assessing 3D printing possibilities for drug production. Producers see

personalized medicine as the answer to their low productivity issue (Big Data Meets Personalized Medicine, 2014).

Regulatory agencies need to guide insurance payments and assess how to comply with existing regulations. Also, providing a new framework for this technology is necessary. The main triggers for accepting any innovation in healthcare are safety and effectiveness.

Pharmacists (hospital and pharmacies). Depending on the positioning of 3D printing in the supply chain, their role would vary from just dispensing the medicines, like now, to personalize them or to completely produce them from scratch.

3D printer suppliers. Their interest is pretty high because their profits will increase tremendously if 3D printers are used for producing drugs. The printer prices are already low enough to enable drug 3D printing; however, as suppliers of the production method, their power is high.

Government's role. Depending on the nation, government's involvement in healthcare is greater or lower. In western countries, its role is mostly as *purchaser and (partial) provider of healthcare* as they pay for the medical services. The extent depends on the country, some governments like the US pay the healthcare to some groups of citizens, while the Spanish government ensures healthcare to all their population. The role can be as a *marketplace regulator*, in these countries like the Netherlands, the government demands their residents to procure themselves with healthcare insurance (Role of Government, n.d.). In the cases where the government fund healthcare by taxation, their role is higher, whereas when they act as regulators, their role is reduced. For this reason, there are two positions in the grid matrix.

Payers. In the healthcare system, the payers include a group of individuals: the government, private health insurance companies and individuals. Their interest is to provide a good healthcare service with the fewest costs possible (less number of tests and visits). Regarding medication, the idea is to use the least quantity possible to cure the disease. Because the benefits of 3D printed medicine will not be recapped sometime after its market introduction, the interest of payers would be to continue delaying its adoption (What is Quality Improvement?, n.d.).

Physicians' role is essential to move from mass-produced medicine to personalized medicine. They can test patients and do the diagnostic themselves or redirect them to pharmacies. Also, their role implies informing patients of the steps that they need to take to get their medicines. If this involves going to the pharmacy or to a drug production point or to take a test in the hospital and after obtaining the results, wait to print the drug. To encourage adoption, a system by which physicians are also reimbursed for using more personalized medicine and diagnostics (Davis, Ma, & Sutaria, 2010).

Patients: 3D printing of drugs is aimed to produce personalized drugs close to the customer reducing costs and waiting times. However, no matter the benefits, the customers' positioning regarding this technology will determine its adoption completely. Most people could call into doubt the credibility and trust of this new system and continue using the "existing" methods (Reads, 2015).

Elderly people who normally take many pills per day, patients with special medication needs (lack of specific enzymes for example) and kids are the patients to benefit most from 3D printing technology. In the case of kids, it is not only the benefit of being able to personalize medicine by printing them with more appealing colours or forms, but also adjusting dosages. The weight of a kid can vary from about 0.5kg to 100kg, thus requiring different dosages. Currently there are no tablets in the market to fit every size of kid (Sanderson, 2015).

Subjects are:

Insurance companies. Some countries lack of healthcare provision, enhancing the importance that insurance companies have. The reimbursement of both the diagnostic tests and personalized medicines would boost the likelihood of their adoption. Although their role is not decisive itself, the decisions made regarding personalized medicine and specially those produced by 3D printing would either promote drug 3D printing or prevent it.

Crowd:

Raw materials suppliers. In the case of manufacturing drugs by 3D printing, the raw materials could either be chemical compounds or inks but their power and interest would remain the same as now. As pointed in some interviews, suppliers can have high bargaining power sometimes. If their bargaining power will increase or lower is unclear, it will depend on the number of suppliers and the importance of the compounds for drug manufacturing.

And *context setters:*

Logistics ensure clinical and economic effectiveness adapting to this new production methodology.

Diagnostic companies will be required to reduce the expensive treatments and the side effects. These companies have everything to gain with personalizing medicine. Their sales will increase enormously as soon as genetic diagnostic are required to produce medicines. Unluckily, the business case for diagnostic tests holds significant risks: high development costs, approval and sale prices. So, still diagnostic companies are not recapping the benefits of the initial investment.

From above, the main conclusion is that key players need to collaborate and be empowered in any decision that is made regarding drug 3D printing. Many key decisions are required which demand the collaboration between stakeholders not only to fulfil their own interest, but also in terms of knowledge sharing. the reason behind it is that what can be a concern for a group of stakeholders, another can provide the solution to it. The winning strategy is to find a way to **combine all stakeholder's opinions and solve the key issues surrounding this new production method**. Also, the other stakeholder's groups need to be listened and their opinions considered as well and involve them in any decision that is being made. After all, all groups of stakeholders with more or less power matter in any decision if its outcome will affect them.

6.3 Corporate responsibility

"Science and technology are not only technical but also socially and politically constituted" (Stilgoe, Owen, & Macnaghten, 2013, p.1569). Understanding this is the basis for responsible innovation.

Corporate responsibility or also referred as responsible innovation is the power to develop technologies but in a responsible way so they do not harm the environment and the society where they are emplaced.

As technologies are embedded in socio-technical systems (spaces where society and technical aspects interact), values and connections to other technologies and stakeholders emerge contingently. Before the new technology gets embedded in the socio-technical landscape, it is important to evaluate the given technology and its alternatives to find the most convenient one. Furthermore, if new technologies fail to take central societal values into account, they may become publicly contested and finally not commercialized or postponed during years. For these reasons, it's essential that engineers adopt an **active responsibility** for their inventions and recognize the **value-laden** character of their **designs** (Pesch, 2015). Adapting the technology to stakeholders' opinions and values increases the likelihood of acceptance and lowers rejection (Esteban, 2015). But more importantly, if scientists want to innovate in a responsible way, public values need to be incorporated in the designs. To fulfil this purpose, whose values need to be considered? (Taebi, Correljé, Cuppen, Dignum, & Pesch, 2014). The stakeholder's analysis in the previous section 6.2 highlighted the society groups whose interests and power regarding drug 3D printing are the highest and thus, need to be taken into account.

Responsible choices can be pursued by analysing the probable future consequences of a given technology and preparing to respond to them. Some of the queries that need to be answered are: "**What other impacts can we anticipate? What don't we know about? What might we never know about? Who will take responsibility if things go wrong**?" (Stilgoe, Owen, & Macnaghten, 2013, p.1570). Stilgoe et al. (2013) has suggested the 4 dimensions of responsible innovation to embed these queries into the innovation process. The first dimension is **anticipation** which consists in foresee the often unforeseen; the experts have to ask themselves, what is known, what is likely, what is possible and what is plausible. One strategy is engaging the key stakeholders in alternative workshops, in which possible alternatives are discussed in a sense that all stakeholders actively participate in the planning process of a new technology. In these workshops, social interactions are simulated to lead to a more effective design, development and implementation process. This methodology is called **constructive technology assessment** (CTA) (Pesch, 2015). Another way that stakeholders can influence the development of this technology is participating in platforms which allows the members to share information and knowledge to stimulate cooperation during research and development phases (Esteban, 2015; Stilgoe et al.,2013). The second dimension is **reflexibility** which challenges assumptions and moral responsibility. The third is **inclusion** which also challenges entrenched assumptions and engage stakeholders in discussion. The last but not the least, **responsiveness** aims to include the ethical values that surround a technology into the development of it (Stilgoe et al.,2013). The system is called **value sensitive design** (VSD) and explores the potential of changing technological features or institutional design characteristics to solve conflicts. A value hierarchy tool is used to transform the stakeholders' values into design requirements that could more easily be included in the technology design (Esteban, 2015; Taebi et al., 2014).

The main values and also concerns surrounding 3D printed medicine are:

- **Full access to healthcare** by everyone: high costs that personalized medicine carries could increase disparity between rich and poor.
- Ensuring **safety and quality** of design. Ensure that the customers are not exposed to any greater risk that they are with the current production processes.
- Enhance human capabilities (less applicable to drug 3D printing, more of biomedical printing)
- Long-term **environmental impacts**
- **National security**: the production of items that are usually under control will be open to the whole public when 3D printers spread (Karagol, n.d.; Dodds, 2015; Neely, 2015)

The stakeholder analysis and responsible innovation stakeholder analysis have pointed the importance of involving the society in the development of a new technology. To ensure the inclusion of stakeholders' opinions and values, two approaches have been suggested that aim to increase society's acceptance, in this case, of drug 3D printing.

6.4 Implementation strategy plan

To enable drug 3D printing become a reality, it would be necessary that:

- **More research is done to solve technical and non-technical challenges.** The current extrusion printers are providing the tools to print drugs. Inkjet are under development due to its increase in complexity possibilities. And other techniques such as fuse filament deposition are also interesting.
- **Production process that produces 3D printed medicines with added value.** Until this moment, no product has arrived to commercialization phase and the most important things is that the added value that 3D printed medicines add is little.
- **Involve stakeholders** with VSD and CTA in order to enhance the technology's possibilities to become adopted and at the same time that it is developed in a responsible way.
- Further develop the **supply chain design alternatives** with real data.

Try-outs in hospitals with special diseases to beta test products: Some experts suggested the strategy to introduce a couple of 3D printers in a research hospital and start personalizing 1 or 2 medications that has been already produced at research facilities. Most probably two of those where a clear diagnostic test does exist to separate patients into groups, with a relative large percentage of patients belonging to each group. Following this criteria, the collaboration with a research facility or a pharmaceutical company to supply the filaments or the inks for the 3D printing production would be most likely. The success of the trial would be higher than starting with drugs tailored to a small population segment and whose diagnostic tests are not well developed yet. After a various number of these trials at different hospitals with diverse 3D printed drugs, a wider production of personalized medicine by 3D printing could be prospected. During these trials, standards, regulation and quality measures could be researched and applied enabling mass drug 3D printing production. At that moment, the diffusion of tailor-made drug 3D printed diffusion will take off.

Figure 45 shows the implementation strategic plan. It consists in 5 stages that show the path to develop drug 3D printing and move from the market adaptation phase towards commercialization. Each phase contains the description, the strategy, the goals and the research required to move towards to following phase.

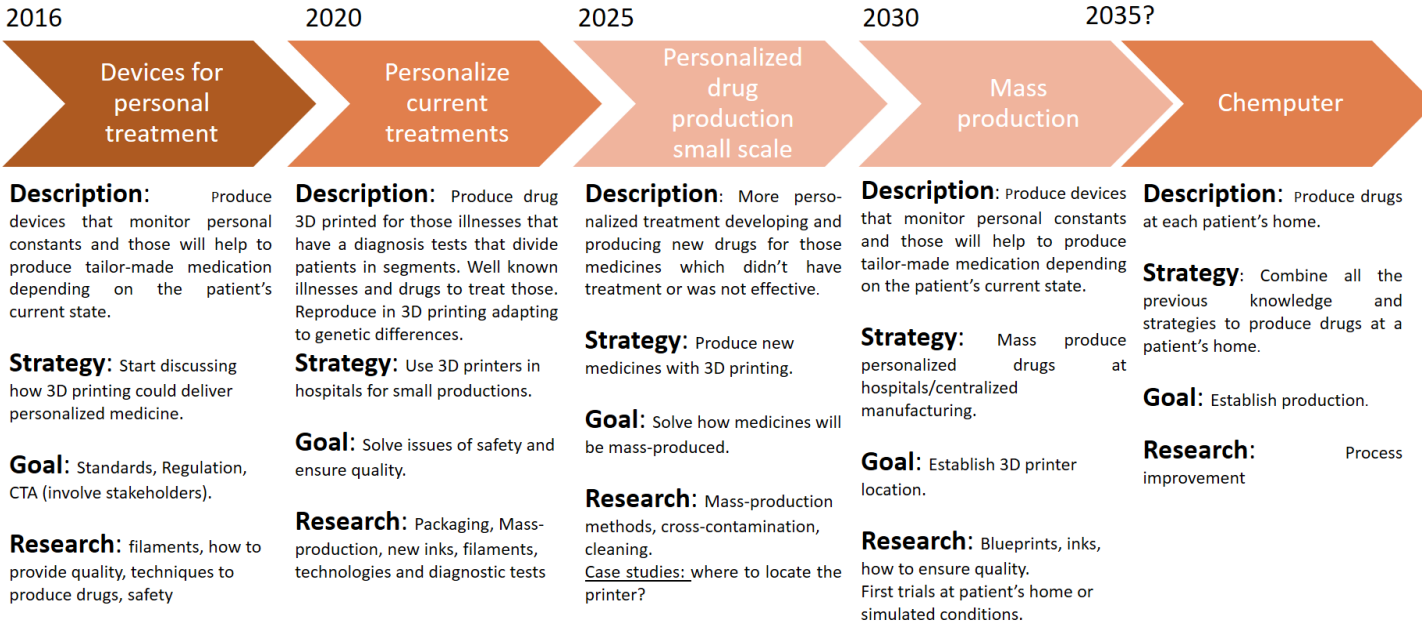

Figure 45 Strategy to develop drug 3D printing and enter the commercial phase. Source: this project.

The implementation strategy showed in figure 45, is a first broad idea that combines research and knowledge collaboration to further develop drug 3D printing into a feasible mass production system and a completely personalized one. Developing devices that control heart rate or glucose concentrations (in case of diabetics) is the first step towards personalized medicine. The other 4 stages in the implementation plan move from initial personalization towards complete tailor-made medicines at each patient's home. The time frame shown is intuitive, according to expert's ideas and articles. The different stages in development and production are necessary because, as previously mentioned, in pharmaceuticals, a clinical success doesn't imply a commercial success (acceptance of population, regulators, etc.). Each phase's goals and research enable the next step of drug printing by solving key challenges and trigger the development of breakthrough innovations. The goals are the requirements to enable drug 3D printing (already pointed in section 5.3.1, at the first stage of the design process). For example, safety and quality issues, standards, 3D printer location, etc. The research section in each stage in the development and application of drug 3D printing process includes all the yet unclear points that need to be solved to apply this technology. For example: how drugs will be packed if mass-produced, how cross-contamination and cleaning be ensured, further development of inks and blueprints, etc.

The first three phases, developing devices for personal treatment, personalize current treatments and small scale 3D printed personalized drugs comprise the 15 years that are necessary to move from the market adaptation stage towards mass production. This was mentioned in the technology adoption section 6.1. These phases represent the consecutive market introductions that will lead to obtain a product that is ready to be mass produced and a technique that complies with all requirements. The last

phase, the chemputer (complete production of the medicines at home just with a set of inks and a blueprint) is the most unknown at this moment due to lack of data, for this reason there's a question mark close to the date.

As already mentioned, the main breakthroughs necessary to enable drug 3D printing become a reality are divided into the different research phases. In the following list they are gathered and explained in detail:

- **Quality and safety measures** that will validate and standardize the production system and then, also accepted by regulators. These include cleaning and cross-contamination free measures.
- **Process validation:** a part of ensuring quality and safety, to validate a process also standards and manufacturing rules such as GMP are necessary. Also, who will be liable in case a drug is not well produced.
- **New packages** if personalized drugs were mass produced.
- **Value-added products:** produce completely personalized medicines. Many of them are under research but they haven't arrived to the commercialization phase. The current medicine produced by 3D printing in the market represents the first step to achieve this goal. This requirement would be achieved at the 3rd stage of the implementation plan in figure 45.
- **Mass-production**: What would the required production volume be? And how would the production in a hospital be achieved? (multi-purpose machines or each machine specialized for a specific drug)

Furthermore, there are some essential **complementary technologies** required to enable personalized drug 3D printing:

a. New materials: New advanced materials for improved delivery of drugs and to produce new drug compositions.
b. Software for generation and management of the 3D printed medication (specifically in the case of producing 3D printed drugs with a chemputer at home).
c. Big data: in order to create the digital thread where the same strand of data is used from the early design to the final production of the product.
d. Biomarkers and sensors to monitor metabolism constants: both systems are necessary for personalized medicine, if the genetic variation of the patient is not known or the heart's rate is not tracked, the doctor will not know which medication specifically that patient needs.

Last but not least, it is essential to bear in mind that pharmaceutical companies are really traditional, more because the high risk involved due to new production methods than because of the high costs. A very conservative attitude is already slowing down the development of drug 3D printing. Most likely, smaller players like start-ups and research laboratories will be the first movers to adopt 3D printing as a production technology and move through the previous mentioned phases. Big pharmaceutical leaders will most likely enter at the second or third stage.

CHAPTER 7. CONCLUSIONS & RECOMMENDATIONS

After designing the pharmaceutical supply chain re-designs, in this section the last design objective will be answered: *What would the strategy of pharmaceutical companies be in the future?* The main research results need to be gathered first so then, develop the product and supply chain managerial strategies. Also, the research contributions and relevance are discussed at the end of the chapter. Figure 46 shows the position of the conclusions in the whole report so it is more clear the process followed.

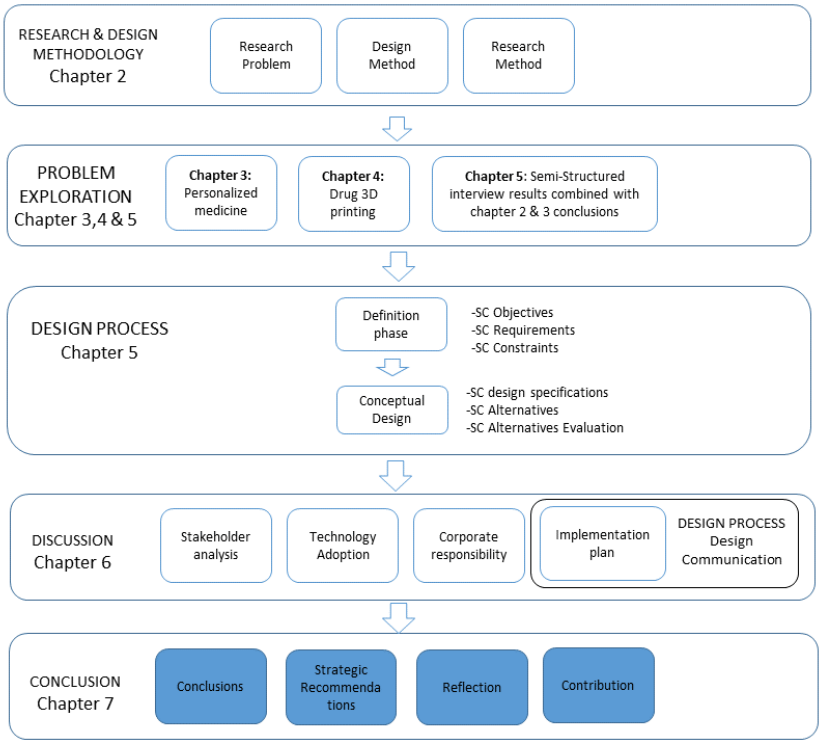

Figure 46 Position of Chapter 7 in the whole research framework. Source: this project

7.1 Conclusions

Personalized medicine represents a step forward in healthcare. It will transform medicine from being reactive to preventive and to a model where each patient gets the pill that best fits his or her needs. Its goal is to provide longer and better life for the patient. It will require diagnostics which link treatment with the disease, to adapt clinical trials to be *N-of-1 trials* which are specific for some population segments and to align the interests behind current system of one-fits-all approach to medicine. Reimbursement of the medical costs and physicians who will need to offer more personalized attention to their patients are critical points for this type of medicine. Moreover, personalized medicine will lower the healthcare costs by reducing the number of unneeded interventions and drug waste on non-responders. Also, the R&D costs will decrease as clinical trials involve less participants and new drugs will be more efficient. However, tailor-made medication is very expensive and not everyone could afford it.

Many sicknesses that require personalized medication such as cardiovascular diseases, diabetes, arthritis, depression and inflammatory diseases can be treated using **solid dosage forms**. With 3D printing, solid pills can be produced with different dosages that adapt to patient's needs at the same time that new

medications can also be manufactured that do not exist with the current methods. The most innovative medication are polypills: a single pill contains multiple APIs. This new form of medication would make patient's life easier, mostly for those patients that need to take many pills per day. At the same time, physicians could ensure that the patient is taking the correct medicine. In principle the production costs are higher for this type of medicines but clinical trials costs and the non-response are lower. Currently, 2/3 of the total medication dispensed are compact dosage formulas that could be 3D printed. Furthermore, big pharmaceutical leaders such as GSK, Pfizer and Roche are pretty interested in drug 3D printing. In the implementation plan, many concerns that require discussion and research have been pointed: how mass-production would be achieved? (multi-purpose machines or each machine will produce a small range of medicines?); how quality and safety will be ensured, packing would be needed? Formulation compatibility in polypills, etc. With the Aprecia pharmaceutical's Spritam®, drug 3D printing production has showed possible, now the main challenges to mass produce them need to be solved and come up with personalized medicine that adds value both for patients and pharmaceutical producers.

The most important points necessary for the development and further adoption of drug 3D printing for personalized drug production are: first of all, **information sharing** between experts. From the interview's analysis one key challenge detected was the lack of alignment between some experts' opinions. For example, regarding counterfeiting, 3D printer speed, accuracy and regulation concerns. A part from opposing views, some experts concerned about expiration date and cross-contamination, whereas others already have the answer to those. This points out a great need for information sharing. In line with this, **stakeholder's involvement** is required to ensure that a technology will develop in a responsible way at the same time that lowers its rejection by the public. The key players in drug 3D printing are pharmaceutical companies (who will produce the inks or filaments and blueprints in a cost effective way), regulatory agencies (provide the regulation and framework required), pharmacists (either in the hospital or pharmacy will produce the drugs), 3D printer suppliers, the government (more or less importance depending their role: marketplace regulator or purchaser), payers, physicians and patients. Furthermore, the main values surrounding this technology should be included to ensure that the main concerns of the population are answered: full access to healthcare for everybody, ensure safety and quality and national security. **Value sensitive design** is a strategy to transform the values into design requirements and this way, introduce them in the technology. After including the values into the design, a panel of discussion with representatives of each stakeholders group would be advisable to understand their opinions and check if their values have already been included. Also, **further research** is necessary to find out how quality and safety could be ensured if the 3D printer is located at the pharmacy or the hospital or at patient's home. Solving the main issues surrounding 3D printing (packaging, cross contamination, process validity) plus providing an added value to the product (medicines that solve existing problems with medication), drug 3D printing will become a reality in a couple of years. **Regulation concerns** such as how to apply current GMP rules, how to adapt them to different countries, how to validate the production process and as mentioned, how to regulate polypills.

After overcoming the main barriers/challenges to main stream this technology (productivity and operating cost lowering), the appropriate strategy is to invest in **complementary technologies** and ensuring quality

and safety, engaging key stakeholders in discussions and knowledge sharing activities to find answers to the key points of drug 3D printing.

From the **supply chain re-design alternatives** analysis is clear that 3D printing can be used to provide completely personalized medicine to each patient by printing his or her medicine at home. Although this alternative increases the pharmaceutical supply chain performance in a greater extent compared with the others, the most likely option in the short term is to print tailor-made medicines at the hospital first and then pharmacies. The first 3D printed medicines would be to cure high insidious diseases where reliable diagnostic tests do already exist. In the short term, the medicines will be produced by extrusion or by ink-jet so either filaments or inks will be required. The inks and filaments would most likely be produced by pharmaceutical companies to maintain their power position. New stakeholders will appear such as 3D printing machine providers and the existent will remain important but their roles will differ.

The entire drug production at home with a *chemputer* is a longer term alternative (around 20 years from now) which requires more research and validation. As the implementation strategy shows (figure 45), firstly devices that help producing personalized treatments will be developed and then drug production with 3D printing will be introduced step by step: first current treatments that require personalization, secondly new personalized treatments and third, mass-production of personalized drugs.

Subsequently, personalized drug 3D printing will enable already in the short term a decentralized manufacture model which will increase the agility and responsiveness of the supply chain. With this model, large inventories will no longer be needed and the production processes will become less complicated with less steps. The supply chain will not only become more agile and responsible, it will increase in efficiency, more flexibility to adapt to customers' needs and become more transparent. Consequently, overall it enhances the main key performance indicators and the closer to customer, the more enhanced they are. Moreover, it will involve less planning and extremely low inventory obsolesce. Regarding manufacture, the consequences of this model are lower lead times, increase value added in production and augmented material efficiency. And the key points regarding delivery are higher order accuracy, on-time delivery and higher product availability with lower inventories (impossible with centralized manufacture models). To sum up, with drug 3D printing, most of the challenges that the supply chain is facing (section 2.1 future challenges) will be overcome evolving towards a new SC structure which is more agile and responsible.

The **decentralized manufacturing model** follows the supply chain trend of redistributing production to lower the costs and fit the demand. It moves from make-to-stock model which requires large inventory levels that can expire after long storage periods, towards a make-to-order model where drugs are produced on demand and send directly to customers. With this model, lives can be saved and reduce each patient's waiting period to get their medication. Increasing visibility through the entire supply chain by computerizing each step, solves two main supply chain issues: traceability and counterfeiting. Also, producing on demand lowers demand volatility risks. In this model it is assumed that API filaments do not expire and the distributed volume fits customer's needs (being directly the patient or the hospital), so non expired or excess product is sent back to the manufacture.

It has been already pointed that although big pharmaceutical companies are researching and developing this technology, is more to assess its opportunities in the market in terms of competitive advantage. This means that big companies will less likely apply the new technology in production in the nearest future. Their strategy is to **wait and see** what the others are doing until the entrance becomes a strategic viable option. In the pharmaceutical field, given the high risk of not getting the products to the market or failing in the commercialization, being the second in the market has greater advantages and thus, great interest for all the players (fast follower advantages). A risk that this strategy has is that other competitors may enter the market first and establish a strong position with high profits and the fast follower struggle to get a share of that market and recap the profits.

Nevertheless, during the innovation and market adaptation phase many alliances are required to establish the new market which solves technological challenges and align the technology with the customers' needs. And most probably, the large pharmaceutical companies will end up buying the diagnostic companies that offer the necessary tests for the drugs that they are selling or/and buy out the small start-up companies that are first in the market as soon as the technology is developed enough to provide a reliable system. The high risks combined with great sunk costs linked to the current production system make the environment hard to adopt this new production method. However, when the companies finally adopt drug 3D printing, the most likely strategy is to leave them as a **new business branch** which will compliment current manufacturing systems. Mainly because it cannot compete with production levels and costs, it offers a new market opportunity: to cover an existing need for a more tailor-made medicine that helps patients to live longer and better.

7.2 Managerial Recommendations

For the pharmaceutical companies that would require a more responsive and agile distribution model in the near future, the drivers will focus on transport and logistics solutions. Giving the competitive environment in which pharmaceutical companies are immersed, a **cost effective supply chain** that provides a greater agility and an improved speed to the market would be the best strategy in the near future (Dijkstral, & Beukema,n.d.; Lofvers, 2013).

A possible strategy is the called **Postponement strategy** which dictates that the firm should postpone the creation or delivery of the final product as long as possible. By doing this, the firm maximizes benefits and lowers risks because the inventory obsolescence and the risk and uncertainties associated with having under stock undesirable products are reduced. However, to ensure that the latest demand forecasts are covered and properly supplied, an integrated and agile supply chain is necessary. In the case of Drug 3D printing, a postponement strategy of the supply chain would fit the business strategy of custom-designed pills for single consumers. 3D printing offers drug personalization an efficient production process that will reduce inventory levels of undesired or no-needed products which is one of the main concerns of drug personalization. In this way, pharmaceutical business model will be entirely demand-driven with the production site located as close to demand as possible ensuring the highest profitability. Nevertheless, a part from being agile, the future pharmaceutical supply chains need to be as lean as possible to maximize efficiency reducing the costs. "Leanness means developing a value stream to eliminate all waste including time, and to enable a level schedule" (Naylor, Naim, & Berry, 1999, p.108). A combination between an agile and lean paradigm will then be the case for pharmaceutical companies (Sehgal, 2010).

With 3D printing as a manufacturing model, a firm can combine both lean and agile strategies in a highly efficient way. The firm can customize production and bringing it closer to customer at the same time that lean times are reduced and resources are used more efficiently (Sehgal, 2010). There are multiple ways to address and make the change that this technology needs in the modern supply chain; no matter how the changes are addressed, what matters is that you have a plan. (3D Printing: The end of the globalised supply chain?, 2012).

According to Deloitte's four strategic paths that enterprises can follow when adopting 3D printing to increase their competitive strength, the long-term strategy that companies most likely will adopt is to **pursuit a completely new business model.** This model modifies both the supply chain and the products that the companies are offering. With this strategy, the manufacturing will take place at the point of use and mass customization will be offered. This is the long-term of personalized drug 3D printing. However, in the short-term, companies are more likely to adapt 3D printing in their current supply chain and offered products but not pursuing any radical change. Corporations will most likely start **producing some of their current products** that would have a market if **personalized, by 3D printing**. In a second step, the companies will move towards offering new products that do not exist before the adoption of 3D printing in order to increase product functionality, market responsiveness and more customization (Marchese, Crane, & Haley, 2015). As already mentioned, 3D printing could either start as a new business branch that complements the existing mass produced products or as a complete new business (most likely this will be the case in start-ups and in the long-term in pharmaceutical companies).

Furthermore, chapter 3 specified the company's required capabilities to enable personalized medicine and chapter 4 the capabilities to do the same for 3D printing. Those highlight the importance of adapting the enterprises' capabilities to enable drug 3D printing. Mainly by encouraging the understanding that personalized medicine is a necessity and reform the company's structure and culture to adapt to it. Some strategies consist in developing a more dynamic and interconnected R&D structure, increase in knowledge exchange between departments and functions and cross-collaboration with other research institutes and enterprises.

7.3 Stakeholder's Recommendations

The suggestions to **drug 3D printing researchers, pharmaceutical companies and regulators** (the three key stakeholders) is to develop more collaborations between them. The reason behind this is that many regulatory points and technical requirements need to be solved to further apply 3D printing technology at the pharmaceutical field. To solve the technical challenges (cleaning and cross-contamination strategies) and the regulatory points (ensure safety, quality) researchers (who have the technical expertise referring to 3D printing), pharmaceutical companies (who have the business strategy and field knowledge) and regulators (who are responsible of providing the rules and standards) need to collaborate. Without collaborating, no further progress would be done in this field as experts are waiting for regulators to determine which are the standards and what needs to be defined to ensure quality and safety. At the same time, regulators are not capable to be up to date with all the innovations that take place at the research centres and the stage of development of those inventions. Meanwhile, pharmaceutical companies will not use a technology that although, it has a huge benefit potential, requires substantial

economic investments and risks. Besides, collaborations with material researchers and 3D printer producers will further develop materials and printers according to drug 3D printing needs.

In a second stage, cooperation with **hospitals and pharmacies** would support the development of the de centralized production model. At this point, the production process would be carried at these locations. As mentioned at the implementation strategic plan, to start the production at these supply chain nodes, firstly, some production try-outs of already existing drugs would be carried and then move towards totally new personalized medicines produced by 3D printing. With this strategy, the last regulation requirements will be defined and customers would become aware of the benefits of personalized 3D printed drugs.

7.4 Research Contribution

This thesis provides two different type of contributions: academic and managerial.

The main academic contribution of this research is **4 supply chain designs where 3D printing is used as a production tool** and how the make and delivery parts of the supply chain are modified. As a secondary contribution, this thesis analyses the rate of adoption of drug 3D printing to produce personalized medicine and the main requirements and complementary technologies that it requires to enter the mass market. It also provides tools (VSD and CTA) to make 3D printing more responsible towards society and environment and to lower its rejection rate.

In addition, the managerial contribution consists in few strategies to bring the current technology towards the commercialization phase with the so called implementation plan and how supply chain should adapt to 3D printing. Also, the stakeholders' recommendations emphasize on the need of collaboration and suggests how to proceed to successfully bring drug 3D printing into the pharmaceutical field.

The **main beneficiaries** of this study are **pharmaceutical supply chain planners and drug and 3D printer researchers.** The first at pharmaceutical companies or external planning enterprises specialized in the pharmaceutical industry, and the latter in research and development institutes (both from drugs and/or 3D printing machines). These strategies will help them understand this technology and its implications in their areas of expertise. In the following section a reflection of the research results (supply chain re-designs and recommendations) will provide insights of the generalizability and applicability of the results.

7.5 Academic Reflection

The main accomplishments in this thesis were the **number of experts interviewed** and the amount of literature found. At the beginning of the research, the main concerns were to find the correct people to approach and get answers from them. In the end, that hasn't been a challenge and instead, it's the most important achievement in this thesis.

Furthermore, as being an initial research about a very innovative topic as drug 3D printing is, the investigation has been mainly qualitative to get a first insight of the subject. Further work is necessary to come up with more detailed design alternatives and establish the likelihood of each of them. As mentioned in the conceptual design section, the 4 alternatives are the most general ones at the moment, but there are many other options where to locate the production with a decentralized manufacturing system. After analysing these general locations, other positions for the 3D printing should be assessed

and compared to the ones shown in this report. Another added value of this research are the design requirements, specifications and performance measures used to evaluate each of the alternative.

A key point of reflection is the possibility to use 3D printing to **produce other types of medicines**. This research was based on using additive manufacturing for a specific production. The reason behind it is that the added value that would bring to the customer is higher. But the reasoning goes further than that because, a part from the customers' willingness to pay for a new medicine type, the companies should be willing to produce them. To do so, the production costs have to be lower than the revenues obtained, and thus just applies to new medicines, not to the manufacture of mass produced drugs like ibuprofen. 3D printing, at least at this moment, cannot compete with existing manufacturing systems in terms of speed and costs so it needs to serve another market.

Another point of reflection is the available techniques to produce 3D printed drugs. At the moment, inkjet and extrusion printers are the most commonly used and with greater future prospects. However, as technology evolves very fast, in the future new techniques might appear that could completely change the current paradigm.

Improvements

Due to the exploratory characteristics of this research, the outcome of it represents an **early design of how the supply chain would look like if 3D printing would be the production method**. Further work would be required to come up with detailed designs and an estimation of which would be the most likely to happen. As mentioned in the design alternatives analysis, the regulator and technical requirements are not fulfilled by the given designs because those terms are not defined yet. For this reason, more knowledge sharing, research and stakeholder involvement are essential to establish those terms and define a detailed supply chain re-design alternatives.

A method that could be used in the future to develop a more detailed design alternatives and compensating the **limitations of SCOR** is Value Sensitive Design (explained in section 6.3 corporate responsibility). In which stakeholder's values are translated into design requirements. Some technical requirements necessary to develop drug 3D printing could have been translated into values for example safety, quality and liability and by this method included in the design.

In order to get a deeper insight on the future alternatives, real data would be required. So, the most convenient would be to carry out a case study in a pharmaceutical company that is already researching on personalized medicine and 3D printing. In a case study, real data could be gathered regarding the performance indicators used in the alternative analysis so a more precise evaluation of each alternative would be provided. In the end, a quantitative evaluation of each alternative would determine which alternative would be the most likely to develop. A **simulation method** would be useful in terms of taking into account the dynamics and efficiency of the supply chain. For example, introducing more detailed performance indicators such as track time, cycle time, effective cycle time, etc. (Chang & Makatsoris, n.d.). However, a first clear understanding of the overall business terms is fundamental: performance measures and production strategy (make-to-stock, make-to-order). And this is what SCOR is for.

Another point of improvement is the **implementation strategy plan**. As mentioned, this is a first idea of how bringing 3D printing from the current adaptation phase towards commercialization. A deeper analysis would provide a more accurate time line and strategies. Also, because technology changes and evolves in an exponential and barely predictable way, the time line is an approximation, it could be that the phases will be partially overlapped or even happening at the same time.

Finding's generalizability

The findings from this report are **not generalizable** for supply chain managers in **emerging economies** such as China. The reason behind it is that the macroeconomic conditions in China and developing countries such as Russia or Brazil differ from the conditions in western countries (EU, US and Japan). For example, the pharmaceutical industry in China is basically formed by stated owned companies with weak international presence. These conditions favour oligopoly (weak international competitiveness and lower market concentration) and state controlled economy (protectionism). Also, governments and State Food and Drug Administration's corruption (Regulatory agency in China for medication and food) and constant policy changes makes impossible the entrance of international companies. Furthermore, another point of differentiation is the restricted reimbursement policies which limit physicians' prescriptions. Health insurance authorities exclude expensive and imported drugs from prescriptions. Only those medications included in the policies are willing to be produced by manufacturers. Another big issue in Chinese pharmaceutical industry is the lack of R&D development as companies do not support it and is based on variations of current medicines and the production of generics(Yu, Li, Shi, & Yu, 2010).

From the distribution point of view, the system is more complex than in the Western countries due to its many different channels; although the main two channels are very similar to Western ones. The main differences are pharmacy lower rates of distribution due to Chinese culture of non-standardized prescription and patient's increased trust on physicians' recommendations and quality assurance at hospitals. And also, as already mentioned, the oligopolistic power of pharmaceutical companies who mostly own the distribution channels (vertically integrated supply chain). The complexity of Chinese supply chain increases the costs of distribution, lowers responsiveness and visibility (Yu et al., 2010). This is not only the situation of China, also the Russian and Brazilian governments favour locally manufactured products and freeze the import of medicines(Ascher, Bogdan, Dreszer, & Zhou, 2015).

To sum up, the macro economic conditions surrounding pharmaceutical supply chain in developing countries lowers the applicability of this thesis results. For this reason, the scope of this report is based on Western Countries plus Japan as the external conditions are very similar. A further analysis would be required to assess how personalized medicine and 3D printing would fit in this landscape. Is it worth mentioning that emerging economies represent an enormous opportunity to increase sales and to grow; however, first, many challenges need to be overcome.

Pharmaceutical field uniqueness

Another reflection point is the **uniqueness of the pharmaceutical supply chain.** The most significant distinctive features surrounding this field are: quality, efficacy, safety, affordability, risk management, diagnosis, complexity (production and distribution), costs (R&D and raw materials) and education. The consequences of not fulfilling high quality, efficacy, safety and low costs requirements are tremendous in

the case of pharmacy enterprises. In other markets like consumable goods like sport shoes or customizable shavers, the consequences are important as well due to its impact on company's reputation and customers' satisfaction. However, any customer's live is at risk. For this reason, pharmaceutical production is under high regulation pressure. Regulation leads to liability aspect. If a product is reported as defective due to its side effects, improperly marketed or defective produced, a player of the supply chain would be held responsible. This could be from the manufacturer, the testing lab, pharmaceutical sales representative, physician, the hospital to the clinic or pharmacy (Janssen, Blankers, Moolenburgh, & Posthumus, 2014; Michon, n.d.). Moreover, affordability is a key element in this field because medication is a need, not a commodity, so everyone should be entitled to get them. Also, the process from discovering a molecule to commercialize a product requires huge investments at the same time that the risks of not getting to the market are extremely high. Diagnosis tests to establish the required treatment for the patient and education to doctors and pharmacists regarding new drugs, side effects and dosage are also necessary. Finally, both production and distribution are complex and expensive due to numerous quality tests, validation of the production methods, stability tests and many supply chain steps.

Another uniqueness point of the pharmaceutical field is **the value chain** (see figure 47)**.** In the current distribution channels, the value in pharmaceuticals is added through all the production phase, distribution and dispensing. In the manufacturing, the added values are innovation (generation of new medicines or in the case of generics, introduction of competition in the market to reduce price margins), regulatory documentation, quality and education. After the medication has demonstrated its principle of action (proof of concept) and it's consequently patented, the value added in the production phase is the maximum. The distribution part ensures continuous supply regardless geographical location and portfolio required, waste management, order processing and education. The main provided value is to meet customers' needs and commercial support required to distribute and sell the medicines. Dispensing to the end customer involves delivering the correct medicine in the correct form and dosage to the right patient.

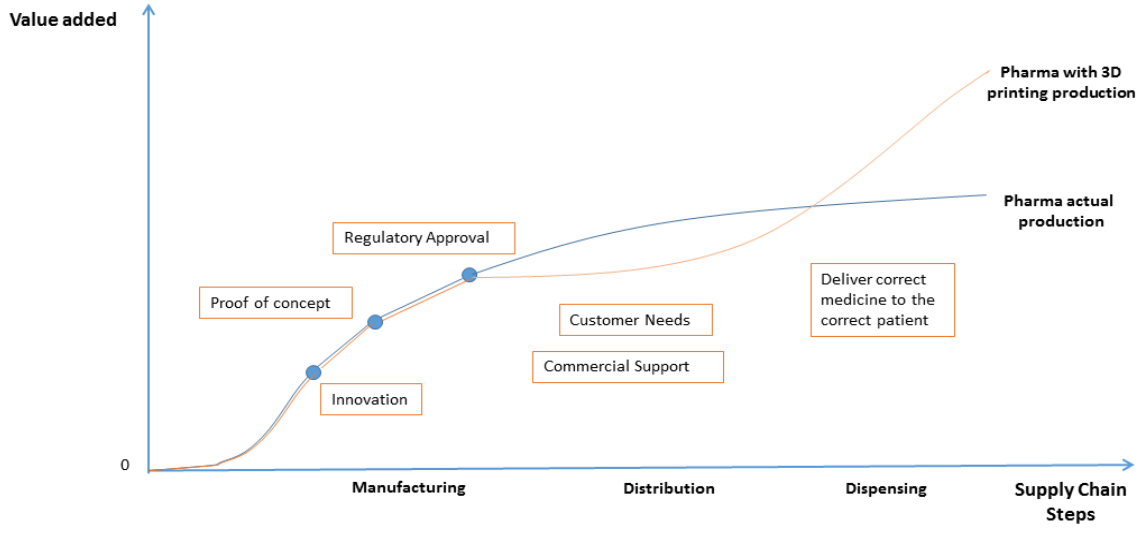

Figure 47 Pharmaceutical value chain in the current production system and with 3D printing. Source: this project.

Is in the dispensing step where most of the value would be added with 3D printing (customized production to fit perfectly customers' needs). With 3D printing the main problematics in dispensing will be solved: unavailability of medicines when ordered and large inventory stocks (IMS institute for Healthcare informatics, 2014). The added value at the manufacturing part would be practically the same cause the APIs and materials still need to be researched, developed and approved for commercialization. However, those steps would be applied on filaments and inks and medication recipes to be introduced in the printers. The distribution's step value is lower than with the actual production methods because with 3D printing, neither commercial support or customer needs is sought in this step. Instead, these two activities are performed at the dispensing stage with more accuracy than with the previous model (that's why the value is higher than in the actual production).

Moreover, the value that 3D printing can provide to the end customer differs from other markets. If pharmacy enterprises are compared with the previous example (consumable goods), 3D printing fulfils a direct need: substitution of the current methods to improve order fulfilment, reduced returns, reduction in complexity and assembly lines and de centralized spare parts productions. In pharma, the benefits in supply chain's performance are clear but to the end customer are vague. The benefits are related to personalizing medicine not to 3D printing itself; in this case, 3D printing is just the production method to enable tailor-made production.

Responsible innovation

Regarding Stakeholder's analysis and responsible innovation, including the main values surrounding a technology as suggested in the conclusion section is not enough. To ensure that a technology is settled in a responsible way, the developers should be able to answer:" What other impacts can we anticipate? What don't we know about? What might we never know about? Who will take responsibility if things go wrong?" (Stilgoe, Owen, & Macnaghten, 2013, p.1570). Despite the identified benefits of drug 3D printing in the pharmaceutical supply chains, what are the **known and unknown risks**? 3DP adoption has advanced exponentially since its invention in the 80s and the previsions are that, although it will not substitute traditional manufacturing methods, it will unquestionably change the existing situation (3D printing: industrial revolution? or hyped technology?, 2016). The already detected risks of drug 3D printing are counterfeiting which has already been explained in detail in section 5.2.1. another risk only mentioned in one literature source was air emissions. Apparently, 3D printers can produce similar air emissions as smoking a cigarette or cooking on a gas stove (Gilpin, 2014). The health and environmental implications of these emissions need to be considered if 3D printing was used to produce large volumes of pills for example in a centralized production model or manufacturing personalized medicines at hospitals. Other perceived risks, which have already been mentioned in section 4.3.6 under 3D printing requirements title, are digital piracy, liability and bioethics; however, the last one do not seem to apply in drug 3D printing at least until now as no human components are included. And the unperceived risks could be none or extremely numerous.

The unpredictability of health and environmental risks is the main challenging factor when a technology tries to enter in the market. Many examples do exist, such as Genetically Modified Organisms or X-ray radiation. In an article published in May in the New York Times called *Genetically Engineered Crops Are Safe, Analysis Finds,* the results of a recent study carried by the US authorities are explained. Those results

deny the health risks that for ages have been attributed to Genetically Modified crops (Pollack, 2016). The common denominator of these risks are its unpredictability in the short term and before the technology enters the market. At the moment, many years need to pass until the effects that a technology has on the society and the environment can be seen. According to some technology ethics school of thought, the unanticipated consequences are due to technology's complexity, dynamics, opaqueness (some elements cannot be seen), ignorance and mistaken assumptions (The Unanticipated Consequences of Technology, 2005). As long as these key factors cannot be overcome, the long term technology risks, would still be unpredictable.

CHAPTER 8. REFERENCES

3D Bioprinting: Medical Applications in 3D Printing. (n.d.). Retrieved April 18, 2016, from https://whalepath.com/challenge/WhdLCpgAW2bt2XEn5/sample/94LTG9dSAjYkvXPif/rev

3D food printing: dichterbij dan menigeen denkt. (2015, April 13). *3D Print Magazine*. Retrieved from http://3dprintmagazine.eu/3d-food-printing-dichterbij-dan-menigeen-denkt/

3D printing: industrial revolution? or hyped technology? (2016). Retrieved April 23, 2016 from https://3dprintingearthblog.wordpress.com/2016/06/01/3d-printing-industrial-revolution-or-hyped-technology/

3D printing for the industry. (n.d.). *3D Print Magazine*. Retrieved May 13, 2016 from http://3dprintmagazine.eu/

3D Printing: The end of the globalised supply chain? (2012). Retrieved May 11, 2016, from http://www.supplychaindigital.com/logistics/3015/3D-Printing:-The-end-of-the-globalised-supply-chain

Anderson, L. (2014). *Drug Expiration Dates - Are Expired Drugs Still Safe to Take?*. Drugs.com. Retrieved March 28, 2016, from http://www.drugs.com/article/drug-expiration-dates.html

Aprecia pharmaceuticals. (n.d.). Retrieved February 22, 2016, from https://www.aprecia.com/about-us/our-mission.php

Arnum, P. Van. (2014). The Future of Dosage Forms. *Pharmaceutical Technology*, *38*(1). Retrieved from http://www.pharmtech.com/future-dosage-forms?pageID=3

Ascher, J., Bogdan, B., Dreszer, J., & Zhou, G. (2015). Pharma's next challenge. *Mckinsey&Company.* Retrieved from http://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/pharmas-next-challenge

Avramenko, Y., & Kraslawski, A. (2008). *Case Based Design: Applications in Process Engineering*. Berlin: Springer. Retrieved from https://books.google.nl/books?id=D-m1OMgxvMIC&printsec=frontcover&hl=ca#v=onepage&q&f=false

Axendia. (2010). *Achieving Global Supply Chain Visibility , Control & Collaboration in Life-Sciences : " Regulatory Necessity , Business Imperative".*

Ayers, A. (2010). Personalized Medicine – Future Impact, Pharma Industry Perspective. *Journal Of Biomolecular Technique*s : JBT, 21(3 Suppl), S5. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2918032/

Ballantyne, C. (2008). In tough times, personalized medicine needs specific partners. *Nature Medicine*, 14(12), 1294-1294. http://dx.doi.org/10.1038/nm1208-1294

Barnatt, C. (n.d.). *Future Technologies: 3D Printing*. Retrieved February 19, 2016, from http://explainingthefuture.com/3dprinting.html

Baumers, M., Dickens, P., Tuck, C., & Hague, R. (2016). The cost of additive manufacturing: machine productivity, economies of scale and technology-push. *Technological Forecasting and Social Change*, 102, 193-201.

Beamon, B. M. (1998). Supply chain design and analysis: Models and methods. *International journal of production economics*, *55*(3), 281-294.

Ben Naylor, J., Naim, M. M., & Berry, D. (1999). Leagility: Integrating the lean and agile manufacturing paradigms in the total supply chain. *International Journal of Production Economics*, *62*(1-2), 107–118. http://doi.org/10.1016/S0925-5273(98)00223-0

Berman, B. (2012). 3-D printing: The new industrial revolution. *Business Horizons*, *55*(2), 155–162. http://doi.org/10.1016/j.bushor.2011.11.003

Big Data Meets Personalized Medicine. (2014). *PharmExec.com*. Retrieved March 17, 2016 from http://www.pharmexec.com/big-data-meets-personalized-medicine

Billam, S. (n.d). Legal issues of 3D printing technology. *ABA Materials.* Retrieved on 14 April from http://www.americanbar.org/content/dam/aba/administrative/litigation/materials/2015_pharma/092915_aba_3D_drug_printing.authcheckdam.pdf

Brandrick, C. (2012). 3D Printer Lets You Print Your Own Prescription. *PCWorld*. Retrieved 18 March 2016, from http://www.pcworld.com/article/254118/3D_printer_lets_you_print_your_own_prescription.html

Bryson, J. M. (2004). What to do when stakeholders matter: stakeholder identification and analysis techniques. *Public management review*, 6(1), 21-53

Burnard, P. (1991). A method of analysing interview transcripts in qualitative research. *Nurse Education Today*, *11*(6), 461–466. http://doi.org/10.1016/0260-6917(91)90009-Y

Campbell, T., Williams, C., Ivanova, O., & Garrett, B. (2011). Could 3D printing change the world. *Technologies, Potential, and Implications of Additive Manufacturing, Atlantic Council, Washington, DC*

Cattell, J., Chilukuri, S., & Levy, M. (2013). How big data can revolutionize pharmaceutical R&D. *McKinsey & Company.* Retrieved February 14, 2016 from http://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/how-big-data-can-revolutionize-pharmaceutical-r-and-d

Cepton. (2007). *Strategic outsourcing across the pharmaceuticals value chain*. Retrieved January 9, 2016, from http://www.cepton.net/publications/download/cepton-Strategic-outsourcing-across-the-pharmaceuticals-value-chain.pdf

Chae, B. (2009). Developing key performance indicators for supply chain: an industry perspective. *Supply Chain Management: An International Journal*,14(6), 422-428.

Chan, I., & Ginsburg, G. (2011). P*ersonalized Medicine: Progress and Promise* (pp. 217–44). Retrieved from http://www.annualreviews.org/doi/pdf/10.1146/annurev-genom-082410-101446

Chang, Y., & Makatsoris, H. (n.d.). Supply Chain Modeling using simulation. *J. of Simulation*, *2*(1).

Chen, I. J., & Paulraj, A. (2004). Towards a theory of supply chain management: the constructs and measurements. *Journal of Operations Management*, *22*(2), 119–150. http://doi.org/10.1016/j.jom.2003.12.007

Christensen, C. M., Grossman, J. H., & Hwang, J. (2009). *The innovator's prescription. A disruptive solution for health care*. New York: McGraw-Hill.

Christopher, M., & Towill, D. (2001). An integrated model for the design of agile supply chains. *International Journal of Physical Distribution & Logistics Management,* 31(4), 235-246.

Clifford, French & Valentine, H. (2010). *Key Methods in Geography*. (2nd edition). SAGE. Retrieved from https://books.google.com/books?hl=ca&lr=&id=bAXmXbF1pkMC&pgis=1

Cohen, D., George, K., & Shaw, C. (2015). *Are you ready for 3-D printing?*. Retrieved 18 March 2016, from http://www.mckinsey.com/business-functions/operations/our-insights/are-you-ready-for-3-d-printing

Cohen, D., Sargeant, M., & Somers, K. (2014). *3-D printing takes shape*. McKinsey Quarterly, Jan.

Consumer health. (n.d.). Retrieved April 15, 2016, from http://www.mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/personalized-medicine/art-20044300

Council, S.-C. (2010). Supply-Chain Operations Reference-model, Scor Overview, version 10.0. *Supply-Chain Council.*

Crawford, M. (2015). *3D-Printed Drugs: What Does the Future Hold?. Asme.org*. Retrieved March 18, 2016, from https://www.asme.org/engineering-topics/articles/manufacturing-design/3Dprinted-drugs-does-future-hold

Davis, D. (2012). *5 strategies to reduce costs and increase efficiency in pharmaceutical R&D.* Retrieved April 20, 2016, from http://www.processexcellencenetwork.com/business-process-management-bpm/articles/5-strategies-to-reduce-cost-and-increase-efficienc/

Davies, C., Baird, L., Jocobson, M. & Tabibkhoei, F. (2014). 3D printing of Medical Devices: When a Novel technology meets traditional legal principles. *Reed Smith: The business of relationships*. [White Paper, 1st Ed.]

Davis, J., Ma, P., & Sutaria, S. (2010). *The microeconomics of personalized medicine*. Retrieved from http://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/the-microeconomics-of-personalized-medicine

De Jouvenel, H. (2000). A Brief Methodological Guide to Alternative Building. *Technological Forecasting and Social Change*, 65(1), 37–48. http://doi.org/10.1016/S0040-1625(99)00123-7

Deloitte. (2014). *2015 Global life sciences outlook*. Retrieved January 10, 2016, from https://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2015-life-sciences-report.pdf

Deloitte Center for Health Solutions. (2009). *The ROI for targeted therapies: a strategic perspective assessing the barriers and incentives for AD*. Retrieved from http://www.theihcc.com/en/communities/supplemental_health/the-roi-for-targeted-therapies-a-strategic-perspec_fr3rq194.html

Deloitte.(2015).*Predictions 2015: 3D printing is a revolution*. Retrieved February 22, 2016, from http://www2.deloitte.com/global/en/pages/technology-media-and-

telecommunications/articles/tmt-pred-3D-printing-is-revolution.html

Dijkstral, E., & Beukema, J. (n.d.). *New challenges for pharmaceutical industry.* Retrieved April 22, 2016, from http://cs.bciglobal.com/news_detail.asp?cat=5002&dc=12097

Dillow, C. (2011). UK Engineers Print and Fly the World's First Working 3-D Printed Aircraft. *Popular Science.* Retrieved February 19, 2016, from http://www.popsci.com/technology/article/2011-07/uk-engineers-print-and-fly-worlds-first-working-3-d-printed-aircraft?cmp=tw

Dockrill, P. (2015). These 3D-printed antimicrobial teeth could one day replace fillings. *ScienceAlert.* Retrieved April 18, 2016, from http://www.sciencealert.com/these-3d-printed-antimicrobial-teeth-could-one-day-replace-fillings

Dodds, S. (2015, February 11). 3D printing raises ethical issues in medicine. *ABC.* Retrieved from http://www.abc.net.au/science/articles/2015/02/11/4161675.htm

Dosage Form Enablers. (n.d.). *Dow.* Retrieved February 23, 2016, from http://www.dow.com/solutions/consumer-and-lifestyle/healthcare-and-medical/drug-formulation-and-delivery/oral-solid-dosage/dosage-form-enablers.htm

Drews, J. (2003). Strategic trends in the drug industry. *Drug Discovery Today*, *8*(9), 411–420. http://doi.org/10.1016/S1359-6446(03)02690-4

Dym, C. L., Little, P., Orwin, E. J., & Spjut, R. E. (2004). *Engineering design: a project-based introduction* (pp. 17-32). New York: Wiley.

Ehrhardt, M., Hutchens, R., & Higgins, S. (2012). Big Pharma's Uncertain Future. *Strategy and business*. Retrived April 7, 2016, from http://www.strategy-business.com/article/00095

Erpelinck, S. (February, 2016). 3D-printing of tablets and opportunities in the field of personalized medicine'. In *3D medicine printing conference.* Conference that was part of 3D Medical Expo, Maastricht, The Netherlands.

Esteban, L. (2015). *A socio and technical map of microalgae as an alternative for fuel production*. Unpublished manuscript, Technical University of Delft.

Esteban, L. (2016). *Managerial implications for additive manufacturing in the pharmaceutical field. Master thesis proposal*. Unpublished manuscript, Technical University of Delft.

FDA. (2015). *What are ´biologics´ questions and answers*. Retrieved March 1, 2016, from http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm

Ferrara, J. (2007). Personalized medicine: challenging pharmaceutical and diagnostic company business models. *Mcgill J. Med*, *10*(1), 59-61.

Fronia, P., Brunner, A., & Nyhuis, P. (2009). Development of a Decision Model for Supply Chain Design. In *Proceedings of the 20th ASOR Conference & the 5th IILS Conference, Surfers Paradise, Australia*.

Gelders, L., Mannaerts, P., & Maes, J. (1994). Manufacturing strategy, performance indicators and improvement programmes. *The international journal of production research*, 32(4), 797-805.

Germen, D. (2016). Chemputer: 3D geprinte medicijnen. *Visionair*. Retrieved February 23, 2016, from http://www.visionair.nl/wetenschap/ted-talk-3D-geprinte-medicijnen/

Gill, P., Stewart, K., Treasure, E., & Chadwick, B. (2008). Methods of data collection in qualitative research: interviews and focus groups. *British Dental Journal*, *204*(6), 291–5. http://doi.org/10.1038/bdj.2008.192

Gilpin, L. (2014). *The dark side of 3D printing: 10 things to watch*. Retrieved June 11, 2016, from http://www.techrepublic.com/article/the-dark-side-of-3d-printing-10-things-to-watch/

Ginsburg, G. S., & McCarthy, J. J. (2001). Personalized medicine: revolutionizing drug discovery and patient care. *TRENDS in Biotechnology*,19(12), 491-496.

Ginsburg, G. S., & Willard, H. F. (2009). Genomic and personalized medicine: foundations and applications. *Translational research*, 154(6), 277-287.

GMP Issues for 3D Printed Pills Resolved But Is It Really a Big Deal. (2015).In *fdamap*. Retrieved May 7, 2016, from http://www.fdamap.com/gmp-issues-for-3d-printed-pills-resolved-but-is-it-really-a-big-deal.html

Gould, S. (2011). *How to write a literature review*. Retrieved June 5, 2016, from http://library.bcu.ac.uk/learner/writingguides/1.04.htm

Gunasekaran, A., Patel, C., & McGaughey, R. E. (2004). A framework for supply chain performance measurement. *International journal of production economics*, *87*(3), 333-347.

Gunderman, R. (2014). The Case for Concierge Medicine. *The Atlantic*. Retrieved from http://www.theatlantic.com/health/archive/2014/07/the-case-for-concierge-medicine/374296/

Hamburg, M. A., & Collins, F. S. (2010). The path to personalized medicine. *New England Journal of Medicine*, *363*(4), 301-304.

Hirshfield, L., Giridhar, A., Taylor, L. S., Harris, M. T., & Reklaitis, G. V. (2014). Dropwise additive manufacturing of pharmaceutical products for solvent-based dosage forms. *Journal of Pharmaceutical Sciences*, *103*(2), 496–506. http://doi.org/10.1002/jps.23803

Hornick, J., & Roland, D. (2013). 3D Printing and Intellectual Property: Initial Thoughts. *The Licensing Journal*, August 2013, 12-16.

Huan, S. H., Sheoran, S. K., & Wang, G. (2004). A review and analysis of supply chain operations reference (SCOR) model. *Supply Chain Management: An International Journal*, 9(1), 23-29.

IMS Institute for Healthcare Informatics. (2014). *Understanding the pharmaceutical value chain*. Retrieved from https://www.imshealth.com/files/web/IMSH Institute/Healthcare Briefs/Understanding_Pharmaceutical_Value_Chain.pdf

Io-Pharma. (2013). *Understanding the Need for Pharmaceutical Supply Chain Visibility*. Retrieved January 9, 2016, from http://www.io-pharma.com/wp-content/uploads/2013/04/iOPharma-Supply-Chain-Visibility.pdf

Janssen, R., Blankers, I., Moolenburgh, E., & Posthumus, B. (2014). *TNO: The impact of 3-D Printing on*

supply chain management. Retrieved from http://3Din.nl/wp-content/uploads/2014/02/TNO-Whitepaper-3-D-Printing-and-Supply-Chain-Management-April-2014-web.pdf

Jenkins, J., Mills, P., Maidment, R., & Profit, M. (2007). *Pharma Traceability Business Case Report*. Retrieved from http://www.bridge-project.eu/data/File/BRIDGE_WP06_Business_Case_Report.pdf

Johnson & Johnson Pharmaceutical Research and Development. (2011). Retrieved April 29, 2016 from http://www.jnj.com/news/all/johnson-johnson-pharmaceutical-research-development-scientists-uncover-previously-unknown-role-for-class-of-molecules

Jonathan, G., & Karim, A. (2016). 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. *International journal of pharmaceutics,* 499(1), 376-394.

Juursema, J. (2015). It's finally here: 3D-printed pills and technology in pharma. *Pharmafile*. Retrieved from http://www.pharmafile.com/news/499162/it-s-finally-here-3d-printed-pills-and-technology-pharma

Kandybin, A., & Genova, V. (2012). Big Pharma's Uncertain Future. *Strategy+Business.* Retrieved March 12, 2016, from http://www.strategy-business.com/article/00095?gko=777a7

Karagol, B. (n.d) *3D printing: What does it offer and for whom?*. TEKPOL Working Paper Series.

Keeling, D., Lösch, M.& Schrader, U. (2010). *Outlook on Pharma operations*. McKinsey & Company.

Keith, J. (2005). The process of design [Power point slides]. Retrieved from http://www.chem.mtu.edu/~jmkeith/arl/2005fall/f05afg2.pdf.

Keskin, B. (2015). *Expert Reveals 7 Supply Chain Trends to Watch.* Retrieved January 10, 2016, from http://www.supplychainopz.com/2015/03/supply-chain-trends.html

Kevin Davies. (2012). Randy Scott: Bringing Metcalfe's Law to Genomic Medicine. *Bio-IT World.* Retrieved January 14, 2016, from http://www.bio-itworld.com/2012/11/30/randy-scott-bringing-metcalfe-law-genomic-medicine.html

King, L. (2015). What is the Engineering Design Process? [Power point slides]. Retrieved from http://www.trinidadstate.edu/pdf/events/soco_2015_08A.pptx. from the course The Engineering Design Process

King, B., & Zhang, X. (2007, April). Securing the pharmaceutical supply chain using RFID. In *Multimedia and Ubiquitous Engineering, 2007. MUE'07. International Conferenc*e on (pp. 23-28). IEEE.

KPMG,. (2012). *Outsourcing in the pharmaceutical industry: 2011 and beyond*. Retrieved from https://www.kpmg.com/Ca/en/IssuesAndInsights/ArticlesPublications/Documents/Outsourcing-pharmaceutical-industry.pdf

Kraljevic, S., Stambrook, P. J., & Pavelic, K. (2004). Accelerating drug discovery. *EMBO Reports*, *5*(9), 837–42. http://doi.org/10.1038/sj.embor.7400236

La vacuna contra el cáncer de cuello de útero, gratis en España desde septiembre. (2008, August 13). *20 Minutos*. Retrived from

http://www.20minutos.es/noticia/405654/0/vacuna/cander/utero/#xtor=AD-15&xts=467263. Retrieved from http://www.20minutos.es/noticia/405654/0/vacuna/cander/utero/

La vacuna del virus del papiloma humano podría erradicar el cáncer de útero en 30 años. (2015,February 12).*20 minutos*. Retrieved from http://www.20minutos.es/noticia/2374821/0/vacuna-vph/papiloma-humano-erradicar/cancer-utero/

Le, B. (2013). 3D Printing Could Revolutionize Drugs. *The Fix*. Retrieved February 22, 2016, from https://www.thefix.com/content/we-could-soon-3d-print-drugs-home91839

Lesko, L. J. (2007). Personalized medicine: elusive dream or imminent reality?. *Clinical Pharmacology & Therapeutics*, 81(6), 807-816.

Linstone, H. A., & Turoff, M. (Eds.). (1975). *The Delphi method: Techniques and applications* (Vol. 29). Reading, MA: Addison-Wesley.

Liotta, L., & Petricoin, E. (2011). Regulatory Approval Pathways for Molecular Diagnostic Technology. *Springer*. Retrieved 15 March 2016, from http://link.springer.com/protocol/10.1007%2F978-1-60327-216-2_27

Lofvers, M. (2013). *New Supply Chain challenges for Pharmaceutical Industry*. Retrieved May 11, 2016, from http://www.supplychainmovement.com/new-supply-chain-challenges-for-pharmaceutical-industry/

Longman, N. (2015). Four Supply chain trends to watch in 2016. *Supply Chain Digital*. Retrieved January 10, 2016, from http://www.supplychaindigital.com/supplychainmanagement/4177/Four-Supply-chain-trends-to-watch-in-2016

Ludema, M. (2015). Supply Chain Mapping with SCOR [Power point slides]. Retrieved from https://blackboard.tudelft.nl from the course Spm4621 Supply Chain Analysis & Engineering.

Manners-Bell, J., & Lyon, K. (2014). The Implications of 3D Printing for the Global Logistics Industry. *Supply Chain 24/7*. Retrieved February 19, 2016, from http://www.supplychain247.com/article/the_implications_of_3d_printing_for_the_global_logistics_industry

Manyika, J., Sinclair, J., Dobbs, R., Strube, G., Rassey, L., Mischke, J., … Ramaswamy, S. (2012). *Manufacturing the future: The next era of global growth and innovation*. Retrieved from http://www.nist.gov/mep/data/upload/Manufacturing-the-Future.pdf

Marchese, K., Crane, J. & Haley, C., (2015). 3D opportunity for the supply chain: additive manufacturing delivers. *Deloitte.* Retrieved on 13 April 2016 from http://dupress.com/articles/additive-manufacturing-3D-printing-supply-chain-transformation/?coll=8717

McKinsey&Co,. (2013). *Personalized medicine. The path forward.*

Melkersson, K. I., Hulting, A. L., & Brismar, K. E. (2000). Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. *Journal of Clinical Psychiatry*, 61(10), 742-749.

Mentzer, J. T., DeWitt, W., Keebler, J. S., Min, S., Nix, N. W., Smith, C. D., & Zacharia, Z. G. (2001). Defining Supply Chain management. *Journal of Business Logistics*, 22(2), 1–25. http://doi.org/10.1002/j.2158-1592.2001.tb00001.x

Meyer, R. (2015). Why 3-D Printed Pills Won't Threaten the Pharmaceutical Industry. *The Atlantic*. Retrieved from http://www.theatlantic.com/technology/archive/2015/08/3d-printing-pills-spritam-drug-industry/401177/

Meyer, J. M., & Ginsburg, G. S. (2002). The path to personalized medicine. *Current Opinion in Chemical Biology*, *6*, 434–438. http://doi.org/10.1016/S1367-5931(02)00340-X

Michon, K. (n.d.). *Product Liability Claims Involving Pharmaceutical Drugs*. Retrieved May 27, 2016, from http://www.nolo.com/legal-encyclopedia/product-liability-claims-pharmaceutical-drugs-30314.html

Miller, G. (2010). Is pharma running out of brainy ideas? *Science*, *329*(5991), 502–4. http://doi.org/10.1126/science.329.5991.502

Miller, H. (2013). Personalized Medicine May Be Good For Patients But Bad For Drug Companies' Bottom Line. *Forbes*. Retrieved from http://www.forbes.com/sites/henrymiller/2013/09/25/personalized-medicine-may-be-good-for-patients-but-bad-for-drug-companies-bottom-line/#44c537791d12

Millsaps, B. B. (2016). Philips Celebrates 125th Anniversary with Pilot Program for 125 3D Printed Shavers, Designed by Consumers. *3DPrint.com*. Retrieved February 19, 2016, from http://3dprint.com/116441/philips-125-3d-printed-shavers/

Min, H., & Zhou, G. (2002). Supply chain modeling: past, present and future. C*omputers & industrial engineering*, 43(1), 231-249.

Mitcheson, J. S., Chen, J., Lin, M., Culberson, C., & Sanguinetti, M. C. (2000). A structural basis for drug-induced long QT syndrome. *Proceedings of the National Academy of Sciences*, *97*(22), 12329-12333.

Müller, J., Pöpke, C., Urbat, M., Zeier, A., & Plattner, H. (2009, September). A simulation of the pharmaceutical supply chain to provide realistic test data. In *Advances in System Simulation, 2009. SIMUL'09. First International Conference* on (pp. 44-49). IEEE.

Murphy, M. (2015). The FDA has approved the first drug made by a 3D printer. *Quartz*. Retrieved from http://qz.com/471030/the-fda-has-approved-the-first-drug-made-by-a-3D-printer/

Neely, E. L. (2015). The Risks of Revolution: Ethical Dilemmas in 3D Printing from a US Perspective. *Science and Engineering Ethics*. http://doi.org/10.1007/s11948-015-9707-4

Okoli, C., & Pawlowski, S. D. (2004). The Delphi method as a research tool: an example, design considerations and applications. *Information & Management*, 42(1), 15–29. http://doi.org/10.1016/j.im.2003.11.002

Ortt, Roland. (2015). Breakthrough Technology Lecture 2B. [Power Point slides]. Retrieved from https://blackboard.tudelft.nl

Ortt, J. R., & Schoormans, J. P. (2004). The pattern of development and diffusion of breakthrough communication technologies. *European Journal of Innovation Management*, *7*(4), 292-302.

Ortt, J. R., Zegveld, M., & Shah, C. M. (2007). Strategies to commercialise breakthrough technologies. *Available at SSRN 1442525*.

Padilla, N., & Kulkarni, A. (2012). A Strategist's Guide to Personalized Medicine. *Strategy+business*. Retrieved 11 March 2016, from http://www.strategy-business.com/article/00131

Padilla, N., & Kulkarni, A. (2014). A Diagnosis for Personalized Medicine. *Strategy+business*. Retrieved 11 March 2016, from http://www.strategy-business.com/article/00248?gko=77033

Palmer, E. (2015). *Gilead's Sovaldi, Harvoni push its full-year sales to $25B; earnings beat expectations*. Retrieved February 23, 2016, from http://www.fiercepharma.com/story/gileads-sovaldi-harvoni-push-its-full-year-sales-25b-earnings-beat-expectat/2015-02-03

Panahiazar, M., Taslimitehrani, V., Jadhav, A., & Pathak, J. (2014, October). Empowering personalized medicine with big data and semantic web technology: promises, challenges, and use cases. In Big Data (Big Data), 2014 IEEE International Conference on (pp. 790-795). IEEE.

Park, R. (2014). Trends in the U.S. IVD Market: Medicare Reimbursement and the Affordable Care Act. *Medical Design Technology*. Retrieved 15 March 2016, from http://www.mdtmag.com/blog/2014/05/trends-us-ivd-market-medicare-reimbursement-and-affordable-care-act

Paxton, A. (2011). Molecular CPT codes topple old 'stacking' codes. *Captodayonline.com.* Retrieved 15 March 2016, from http://www.captodayonline.com/Archives/0411/0411d_molecular_cpt.html

Pelzel, K. (2015). What's Next for the Pharmaceutical Supply Chain? *Inventory & Supply Chain Optimization*. Retrieved from http://www.inventory-and-supplychain-blog.com/whats-next-for-the-pharmaceutical-supply-chain/

Pennic, J. (2014). Infographic: The Rise of Personalized Medicine. *Hitconsultant.net*. Retrieved 4 March 2016, from http://hitconsultant.net/2014/04/03/infographic-the-rise-of-personalized-medicine/

Pesch, U. (2015). Engineers and Active Responsibility. *Science and Engineering Ethics*, *21*(4), 925–39. http://doi.org/10.1007/s11948-014-9571-7

Phillips, W. (2016, January 29). Redistributed Manufacturing in Healthcare Network (RiHN) [video file]. Retrieved from https://www.youtube.com/watch?v=trDdd4oo8q4

Pollack, A. (2016). Genetically Engineered Crops Are Safe, Analysis Finds. *The New York Times*. Retrieved from http://www.nytimes.com/2016/05/18/business/genetically-engineered-crops-are-safe-analysis-finds.html?rref=collection%2Ftimestopic%2FGenetically Modified Food&action=click&contentCollection=timestopics&region=stream&module=stream_unit&version=latest&conten

Ponis, S. T., & Koronis, E. (2012). Supply chain resilience: definition of concept and its formative elements. *Journal of Applied Business Research*, *28*(5), 921

Predictions 2015: 3D printing is a revolution. (2015). Retrieved February 22, 2016, from http://www2.deloitte.com/global/en/pages/technology-media-and-telecommunications/articles/tmt-pred-3d-printing-is-revolution.html

Preis, M., Breitkreutz, J., & Sandler, N. (2015). Perspective: Concepts of printing technologies for oral

film formulations. *International Journal of Pharmaceutics*, *494*(2), 578–84. http://doi.org/10.1016/j.ijpharm.2015.02.032

Privett, N., & Gonsalvez, D. (2014). The top ten global health supply chain issues: perspectives from the field. *Operations Research for Health Care,* 3(4), 226-230.

Process, method and benefits. (n.d.).*EOS Industrial 3D printing*. Retrieved February 19, 2016, from http://www.eos.info/additive_manufacturing/for_technology_interested

Programma: Personalised Medicine. (n.d.). Retrieved April 15, 2016, from http://www.zonmw.nl/nl/programmas/programma-detail/personalised-medicine/actueel/

PWC. (2012). *Pharma 2020*: *From Vision to Decision.* PWC Pharma 2020. Retrieved from http://www.pwc.com/gx/en/pharma-life-sciences/pharma2020/vision-to-decision.jhtml

Reads, H. (2015). The Big Ideas 3D-Printing Brings to Big Pharma. *Huffingtonpost*. Retrieved February 23, 2016, from http://www.huffingtonpost.com/hippo-reads/the-big-ideas-3dprinting-_b_8790918.html

Roberts, C. (February, 2016). 3D printing a functional polypill: a practical manufacturing method? In *3D medicine printing conference.* Conference that was part of 3D Medical Expo, Maastricht, The Netherlands.

Robinson, A. (2015). Welcome to the complex world of 3D-printed drugs. *The Guardian*. Retrieved from http://www.theguardian.com/sustainable-business/2015/aug/21/welcome-to-complex-world-of-3d-printed-drugs-spritam-fda

Rocky Mountain Technical Marketing, Inc. (n.d.) *Supply-Chain Integrity*. Retrieved March 13, 2016, from http://www.rmtminc.com/page/product-solutions/supply-chain-integrity.html

Role of Government. (n.d.). Retrieved May 9, 2016, from http://healthactionnetwork.com/issues.aspx?IssueID=TheRoleofGovernment

Rossetti, C. L., Handfield, R., & Dooley, K. J. (2011). Forces, trends, and decisions in pharmaceutical supply chain management. *International Journal of Physical Distribution & Logistics Management*, 41(6), 601-622.

Rouse, M. (2009). *What is supply chain visibility (SCV)?.* Retrieved January 9, 2016, from http://searchmanufacturingerp.techtarget.com/definition/supply-chain-visibility-SCV

Rusu, A., Kuokkanen, K., & Heier, A. (2011). Current trends in the pharmaceutical industry – A case study approach. *European Journal of Pharmaceutical Sciences*, *44*(3), 437–440. http://doi.org/10.1016/j.ejps.2011.07.008

Sanderson, K. (2015). 3D printing: the future of manufacturing medicine?. *Pharmaceutical journal.* Retrieved February 23, 2016, from http://www.pharmaceutical-journal.com/news-and-analysis/features/3d-printing-the-future-of-manufacturing-medicine/20068625.article

Sandler, N. (2015, December 8), 3D Printing Drugs. [Video]. Retrieved from https://www.youtube.com/watch?v=kfhyNZY9Idk

Sandler, N. (February, 2016). Printing technologies in fabrication of drug delivery systems. In *3D medicine printing conference.* Conference that was part of 3D Medical Expo, Maastricht, The

Netherlands.

Schork, N. J. (2015). Personalized medicine: time for one-person trials. *Nature*, 520(7549), 609-611.

Schuhmacher, A., Germann, P.-G., Trill, H., & Gassmann, O. (2013). Models for open innovation in the pharmaceutical industry. *Drug Discovery Today*, 18(23-24), 1133–7. http://doi.org/10.1016/j.drudis.2013.07.013

Second Redistributed Manufacturing Healthcare Research Network (RiHN) workshop. (2015). Retrieved April 21, 2016, from https://capturingthevalue.wordpress.com/2015/03/25/second-redistributed-manufacturing-healthcare-research-network-rihn-workshop-28-april-2015/

Sehgal, V. (2010). *Supply Chain Management: Postponement as Supply Chain Strategy*. Retrieved May 11, 2016, from http://www.supplychainmusings.com/2010/10/postponement-as-supply-chain-strategy.html

Sekaran, U. (2006). *Research methods for business: A skill building approach*. John Wiley & Sons.

Shah, N. (2004). Pharmaceutical supply chains: key issues and strategies for optimisation. *Computers & chemical engineering*, *28*(6), 929-941.

Shang, W. (February, 2016). The regulatory perspective: benefits and limits of 3D printed drugs. In *3D medicine printing conference*. Conference that was part of 3D Medical Expo, Maastricht, The Netherlands.

Shapiro, C., & Varian, H. R. (1999). *Information Rules: A Strategic Guide to the Network Economy*. Harvard Business School Press. Retrieved from https://books.google.com/books?id=aE_J4Iv_PVEC&pgis=1

Shepherd, C., & Günter, H. (2010). Measuring supply chain performance: current research and future directions. In *Behavioral Operations in Planning and Scheduling* (pp. 105-121). Springer Berlin Heidelberg.

Staton, T. (2014). Who are the stars of personalized medicine? Roche, Novartis and J&J. *Fierce Pharmamarketing*. Retrieved from http://www.fiercepharmamarketing.com/story/who-are-stars-personalized-medicine-roche-novartis-and-jj/2014-11-26

Stilgoe, J., Owen, R., & Macnaghten, P. (2013). Developing a framework for responsible innovation. *Research Policy*, *42*(9), 1568–1580. http://doi.org/10.1016/j.respol.2013.05.008

Szczerba, R. J. (2015). FDA Approves First 3-D Printed Drug. *Forbes*. Retrieved from http://www.forbes.com/sites/robertszczerba/2015/08/04/fda-approves-first-3-d-printed-drug/#2c2ba19d2c8a

Table of Pharmacogenomic Biomarkers in Drug Labeling. (2015). Fda.gov. Retrieved 15 March 2016, from http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

Taebi, B., Correljé, A., Cuppen, E., Dignum, M., & Pesch, U. (2014). Responsible innovation as an endorsement of public values: the need for interdisciplinary research. *Journal of Responsible*

Innovation, *1*(1), 118–124. http://doi.org/10.1080/23299460.2014.882072

Tata consultancy services. (2015). Retrieved February 28, 2016 from http://www.tcs.com/Pages/default.aspx

Teva Pharmaceutical industries Ltd., (2015). Retrieved January 16, 2016 from http://www.tevapharm.com/

The benefits of personalized medicine. (n.d.). Retrieved April 15, 2016, from https://www.jax.org/genetics-and-healthcare/personalized-medicine/benefits-of-personalized-medicine#

The Unanticipated Consequences of Technology. (2005). Retrieved June 11, 2016, from https://www.scu.edu/ethics/focus-areas/more/technology-ethics/resources/the-unanticipated-consequences-of-technology/

Thomas, K. (2016). The price of health: the cost of developing new medicines. *The Guardian*, *Healthcare*. Retrieved from http://www.theguardian.com/healthcare-network/2016/mar/30/new-drugs-development-costs-pharma

Tillmann, V., Patel, L., Gill, M. S., Whatmore, A. J., Price, D. A., Kibirige, M. S., ... & Clayton, P. E. (2000). Monitoring serum insulin-like growth factor-I (IGF-I), IGF binding protein-3 (IGFBP-3), IGF-I/IGFBP-3 molar ratio and leptin during growth hormone treatment for disordered growth. Clinical endocrinology, 53(3), 329-336.

TNO working on personalized 3D printed oral dosage drugs, Steven Erpelinck reveals. (2016). Retrieved April 18, 2016, from http://www.3ders.org/articles/20160229-tno-working-on-personalized-3d-printed-oral-dosage-drugs-steven-erpelinck-reveals.html

University of Sussex. (n.d.). *Pharma Supply Chains and Healthcare Technology.* Retrieved April 20, 2016, from http://www.sussex.ac.uk/pharmasystems/

van Noort, R. (2012). The future of dental devices is digital. *Dental Materials : Official Publication of the Academy of Dental Materials*, *28*(1), 3–12. http://doi.org/10.1016/j.dental.2011.10.014

Ventola, C. L. (2014). Medical Applications for 3D Printing: Current and Projected Uses. *P & T : A Peer-Reviewed Journal for Formulary Management*, *39*(10), 704–11. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4189697&tool=pmcentrez&rendertype=abstract

Verschuren, P., Doorewaard, H., & Mellion, M. (2010). *Designing a research project* (Vol. 2). The Hague: Eleven International Publishing.

Vijverman, A. (February, 2016). Legal Issues around 3D Printed Drugs. In *3D medicine printing conference*. Conference that was part of 3D Medical Expo, Maastricht, The Netherlands.

Wang, Y. (2013). *Supply Chain Management: Demand and Supply Planning in Pharmaceutical Industry.* Retrieved May 8, 2016, from http://cmuscm.blogspot.nl/2013/09/demand-and-supply-planning-in.html

What is Clinical Decision Support (CDS)?. (2013). *Healthit.gov*. Retrieved 11 March 2016, from https://www.healthit.gov/policy-researchers-implementers/clinical-decision-support-cds

What is 3D printing? How does 3D printing work? (n.d.). Retrieved February 19, 2016, from http://3dprinting.com/what-is-3d-printing/

What is Quality Improvement? (n.d.). Retrieved May 9, 2016, from http://patientsafetyed.duhs.duke.edu/module_a/introduction/stakeholders.html

What is Roche Personalised Healthcare all about? (n.d.). Retrieved April 15, 2016, from http://www.roche.com/about/priorities/personalised_healthcare/what_is_roche_personalised_healthcare_all_about.htm

WHO. (2016). *Pharmaceutical Industry.* Retrieved April 24, 2016 from http://www.who.int/trade/glossary/story073/en/

Williams, D. (n.d.). Clinical Trial Innovation. *Janssen*. Retrieved November 9, 2015, from http://www.janssen.com/clinical-trials/innovation

Yeston, J. (2016). Drug manufacturing in a fridge-sized box. *Science*,352(6281), 48-48.

Yeung, K. (2016). *Leeo's smart alert monitor will now tell you if there's rain in the forecast.* Retrieved February 23, 2016, from http://venturebeat.com/2016/02/23/leeos-smart-alert-monitor-will-now-tell-you-if-theres-rain-in-the-forecast/

Yu, X., Li, C., Shi, Y., & Yu, M. (2010). Pharmaceutical supply chain in China: current issues and implications for health system reform. *Health Policy (Amsterdam, Netherlands)*, *97*(1), 8–15. http://doi.org/10.1016/j.healthpol.2010.02.010

Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., & Friedman, J. M. (1994). Positional cloning of the mouse obese gene and its human homologue. *Nature*, 372(6505), 425-432..

Zott, C., & Amit, R. (2008). The fit between product market strategy and business model: implications for firm performance. *Strategic management journal*, 29(1), 1-26.

CHAPTER 9. APPENDIX

PART A

Trends in the pharmaceutical supply chain

Cross-industry collaboration: open innovation

As explained in the introduction of this report, the development of new products is getting more and more complicated: the emerging new technologies, the availability of highly qualified experts outside the existing medical companies and the increased pressure on time and cost might have pushed the development of open innovation. Open innovation consists in that firms use both internal and external ideas and paths to market to advance their technology. For this reason, companies are changing the way that business was done until this moment. The old system in which the big pharmaceutical companies played the central part of drug innovation is moving to a decentralized system where all the companies will be responsible for the worldwide development and marketing of widely used drugs(Drews, 2003).

Companies now see the opportunities of sharing knowledge with other enterprises in the same business group. But not only that, they are partnering with other industry consortiums and third-party vendors. For example, Janssen biologics has pursued a novel cross-industry collaboration with Merck, Pfizer, Eli Lilly and Novartis. They have formed a shared repository with key information about Good Clinical Practice (GCP) training records, clinical trial sites, trial participation and recruitment history. The advantage of this platform is the ability to easy access to this information. In this way, the time-consuming work required to gather all the information from different clinical trial sites is cut out (Williams, n.d.).

Randy Scott, CEO and founder of InVitae once said that Pharmaceutical companies need to realize that information is more valuable when it is shared. This is because due to Metcalfe's Law[5], if pharmaceutical companies open source their numbers from clinical trials and innovation efforts, it will be a significant boost to innovation; which depictures the current need for open innovation(Davies, 2012).

At this moment, multinational pharmaceutical companies have started to realize and exploit the full potential of open innovation. If a R&D project portfolio is analyzed, you will notice that it comprises nearly 50% externally developed projects (Schuhmacher, Germann, Trill, & Gassmann, 2013). How knowledge sharing will affect big pharmaceutical leaders? What are the consequences of this in the supply chain of these companies?

Emerging markets

With today's slow down economic growth, companies' need to find other places to invest. Emerging markets, in the so-called developing countries, are predicted to grow twice to three times faster than countries like Europe or the US. As they are becoming the driver of global growth, they represent a very interesting opportunity for investors (Drews, 2003).

[5] *Metcalfe's law* establishes that "the value of a network goes up as the square of the number of users" (Shapiro & Varian, 1999, p.184).

On one hand, developing countries represent a big opportunity as these markets expand rapidly but on the other hand, they come with many challenges. These countries have different geographical size, culture, underdeveloped infrastructure, fragmented distribution systems and weak regulations. Thus, companies that want to operate in these markets need to adapt their strategies(FDA, 2015).

And so forth, how have the industry main players responded until now? According to PWC (2012), they've adopted four different strategies. Some, like Roche, which are the most innovative, have concentrated on quality rather than quantity. Others, have adopted the opposite strategy; these companies have focused on increasing sales volume and market share. Their strategy consisted in offering primary-care products with differential pricing and getting a strong position regarding generics by constructing generics divisions in key territories. For example GSK exemplifies this approach(PWC, 2012). The other leading players have positioned themselves somewhere between these two extremes. Eli Lilly, for example, has focused on selling branded medicines. Sanofi, on the contrary, has invested heavily in the generics market. Besides Merck & Co lies in the middle. Their approach is building on partnerships with companies that are already working in these markets; for example they partnered with Sun Pharma, an Indian generics producer (PWC, 2012). Do these policies have an effect on these companies supply chain?

Increase visibility and traceability

Growing globalization increases the complexity of the enterprise and transforms the traditional single supply chain into a complex supply network.

Following from Axendia[6]'s report in which the future trends and changes in the Supply chain are analysed, there's a need for companies to shift to intelligent supply networks that provide information on-demand instead of continuing interpreting the supply chains from a supplier–buyer point of view. In a supply chain network, collaboration occurs during the entire product life cycle, from the raw-material supplier to the delivery company that distributes the end product to the user(Axendia, 2010).

The main treats against quality and control that pharmaceutical companies are envisioning for the next years are counterfeits, product customization and lack of ability to trace products. The FDA is well aware of the patient safety benefits of traceability systems. Already by the end of 2003, FDA encouraged the use of track and trace technologies to lower the risk of the counterfeit threat (Jenkins, J., et al., 2007). Weak or incomplete security is exacerbating the spread of counterfeit drugs, particularly in emerging markets. In emerging countries the most counterfeited medicines are those used to cure life-threatening conditions such as malaria, tuberculosis, and HIV/AIDS. Tuberculosis and malaria counterfeits are estimated to kill some 700,000 people a year(Deloitte, 2014).

A part from fighting against counterfeit drugs, the industry should better manage and control their supply chain. This can be done by increasing on-demand visibility. Supply chain visibility (SCV) can be defined as the control over specific information related to product orders and products in transit from the producer to their final destination. By strengthening the supply chain visibility, data is made available to all

[6] *Axendia* is a strategic business consultancy based in the US specialized in Life-science and healthcare markets(Axendia, 2010).

stakeholders (iOPharma, 2013, 2013; Rouse, 2009). Furthermore, enterprises can change the view of your company's supply chain to a supply network; and reinforce collaboration.

Regarding visibility, there are many current and innovative technologies that can be used in order to track products. The most promising are: linear bar codes such as the SSCC for logistics unit identification, RFID codes, SGTIN for mass serialization, batch number and expiry date information and the use of the Electronic Product Code(Jenkins et al., 2007). With these technologies, goods will transmit their location all the time, so they will no longer be lost or misplaced in transit(Jenkins, J., et al., 2007).

Opportunities by outsourcing

In the past, pharmaceutical companies use to manufacture all the products in-house and they were reluctant to share information or resources with other players. However, the past situation has changed; internal resources are getting exhausted and their product pipeline is getting thinner and thinner. To overcome this situation and reduce costs, pharmaceutical firms are outsourcing jobs such as manufacturing, packaging, research and sales. And this trend will increase dramatically the following years: the U.S. market for subcontracted pharmaceutical production will grow up to 10 to 12% annually.

For instance, GlaxoSmithKline, Novartis and Schering started outsourcing real state and facility management segments in 1999. Furthermore, companies like AstraZeneca and Astellas started outsourcing their information technology infrastructure two years later. In 2002, J&J was the first pharma company to outsource its administration and accounting; it was also the first to engage in legal process outsourcing in 2006. The same year GlaxoSmithKline and Pfizer embraced finance and accounting outsourcing(KPMG, 2012).

However, not only administrative jobs are being outsourced, nowadays companies are moving to outsource production and R&D. By outsourcing, companies can increase their know-how by accessing to external knowledge that they do not possess (Schuhmacher et al., 2013). Nevertheless, to cut-off costs, R&D outsourcing involves contracting academic researchers and small biotech companies to perform the early stages of drug research that was formerly done in-house. One common trend is outsourcing R&D to China, Latin America and other Eastern countries. To give an example, AstraZeneca and GSK both set up R&D centers in Shanghai, China, in 2007 (G. Miller, 2010). A part from reducing costs and increasing knowledge, outsourcing R&D offers a dubious practice that is to perform drug testing in those regions where there are huge patient pools with large treatment-naïve population and a western-like epidemiology. There are drawbacks too, cultural, language differences and regulatory barriers do exist. Another possibility to reduce development costs is to in-license possible candidates in early development stages instead of focusing on developments coming from internal research departments.

The trend of outsourcing doesn't stop here, another part of the business that hasn't been outsourced until now is manufacturing. Today nearly one third of the pharmaceutical industrial output ($130bn) is produced via contract manufacturing organizations. The current trend is this third parties provide complete customizable solutions instead of just manufacturing process (Cepton, 2007).

How can companies in-license or out-source? There are many answers of how they do it; the main ones include purchasing, capability bartering, risk sharing and financial hedging. The first option, purchasing is a valid model for companies having capital available but only limited resources, capabilities or certain skills. Bartering consists in companies offering their own resources (laboratory capacity, data bases, genome-models, in-silco testing, etc.) to small companies which would otherwise not have access to those resources. Thereby, large companies support early stage cooperation with small enterprises. Financial Hedging consists in using outside capital that needs to be paid back with interests. And finally, risk sharing consists in outsource early stages of development to other companies. In case of a positive proof of concept pharmaceuticals companies are allowed to buy back product rights.

By outsourcing, a part from the benefits already mentioned, companies can focus more on other strategic activities and get more flexibility. Nevertheless, these potential gains have to be balanced with the loss of know-how and the need of quality control. For this reason, the decision whether to outsource o not and if so, which parts, demands an in-depth study of the company's core competencies, value chain and future strategies.

Personalized medicine

Personalized medicine consists in targeting the practice of medicine to each patient. Instead of diagnosing the illness and give a treatment, doctors target the therapy to an individual's molecular profile by using marker-assisted diagnosis and targeted therapies. Thus, clinical diseases will be replaced by molecular classification and therapies will be directed to the root of the illness. Homogeneous clinical phenotypes will require different treatment strategies. Thus, techniques such as screening, molecular predisposition, diagnostic, pharmacogenomics, prognostic and monitoring markers are required to find person's unique clinical, genetic, environmental and genomic information. Molecular understanding of illnesses will allow to optimize not just curative care but also preventive medicine. This type of medicine treatments offers the possibility to treat people while they are still healthy or at the earliest stages of disease. This strategy opposes the traditional model of reactive healthcare which intervenes after the disease has manifested in the patient (Ginsburg, G. S., & Willard, H. F., 2009; Ginsburg, G. S., & McCarthy, J. J., 2001).

The promise of tailoring the medicine to individuals will change drastically the healthcare as we know it: the trial-and-error practice of medicine will disappear and it will open the door to a preventive and proactive healthcare. Targeting treatments to patients' needs will allow physicians to make the right patient-care decisions and for the patients, to make informed decisions with full information (Ginsburg, G. S., & McCarthy, J. J., 2001). The final goal of personalized medicine is to optimize medical care for each individual, including treatments, dosages, medication types and prevention strategies resulting in a total customization of patient care.

Custom medicine will need the collaboration of multidisciplinary health care teams in order to promote patient education and satisfaction, health and wellness, and personalized disease detection, prevention and treatment (Ginsburg, G. S., & Willard, H. F., 2009).

Strategic decisions Pharmaceutical companies

The strategic decisions that a company needs to take considering its business process and the key performance measures include:

- Plan: **Capacity planning** and network design of the plant and supply chain and plant design: establish the required equipment and storage. These decisions are quite uncertain due to long lead times to make capacity effective. Demand uncertainty and pipeline uncertainty are the two key issues that mostly affect capacity planning. The first, is because competition and uncertainty regarding patent protection. The second one, because it is uncertain which drugs will succeed to reach the market and which not.
- Source: **Suppliers choice.**
- Make: **Pipeline and development management**: selection of potential drugs to develop further, and the planning of their development. **Process development**: establishing the manufacturing routes and the manufacturing processes. It is driven by chemistry and yield optimization. Inefficiencies in this stage results in long cycle times due to processes that are operated much more slowly than the intrinsic rates. **Plant design**: select the required equipment and storage units.
- Delivery: **Network design**. Depending on the product and localization, the supply chain results to be more or less complicated (Shah, N., 2004).

Personalized medicine

Diagnosis

A patient's response to a medication is a complex combination of non-genetic and genetic factors. Many molecules present in the human body can be used as efficacy or toxicity predictors such as disease pathways, drug-metabolizing enzymes or genetic variants in the drug target (Ginsburg, G. S., & McCarthy, J. J., 2001; Ginsburg, G. S., & Willard, H. F., 2009).

Biomarkers

Many clinical and pre-clinical studies are studying co-regulated genes and targets to use them as biomarkers in drug development stages. Ideal markers are the ones that can be easily detected by mass-spectroscopy or antibody detection methods such as secreted and cell-surface proteins. One example of biomarker is the gene that encodes the protein leptin, which is a body fat regulator that can be used to monitor the body's response to the treatment with growth-hormone in kids (V. Tillmann, et al., 2000; Y. Zhang, et al., 1994; K.L. Melkersson, et al., 2000).

Other biomarkers are toxicogenomic indicators which are used to predict adverse drug reactions (ADRs) in the following discovery steps. Many companies already showed their interest in pharmacogenomics. Some are already starting developing gene expression-based assays to test preclinical compounds regarding their propensity to introduce ADRs (Ginsburg, G. S., & McCarthy, J. J., 2001; Ginsburg, G. S., & Willard, H. F., 2009).

Additionally, since 1999, a consortium of companies and research institutes are mapping the most common genetic variation: SNPs. A SNP map will facilitate the identification of genes involved in complex

diseases like asthma, psychiatric disorders and diabetes mellitus. Furthermore, as explained in the previous section 3.2.4, clinical trials are being re-designed to allow DNA storage and its information used in the development and discovery phases (Ginsburg, G. S., & McCarthy, J. J., 2001; Ginsburg, G. S., & Willard, H. F., 2009).

Apart from introducing genomic tests in drug R&D phases, companies are producing direct-to-consumer initiatives to make each patient's genome variation available directly to them. The service/product consists in information from 20 to 80 genome areas identified as loci susceptible to disease and information of the patient's ancestors. This innovation will provision of disease risk information to customers directly without any doctors' involvement so it's considered as a completely "disruptive technology". Nevertheless, as all innovative technologies, this product carries many challenges and ethical concerns that need to be measured (Ginsburg, G. S., & McCarthy, J. J., 2001; Ginsburg, G. S., & Willard, H. F.,2009).

In the long term, advances in the understanding of linkages between genotypic and proteomic markers and disease will make genomic tests clinically applicable and relevant, increasing their use and impact on healthcare outcomes.

Customize patient's treatment

In order to customize each patient's treatment, some tools to provide personal health risk information are needed. The first of them is **Family health history** which reflects the combination of genetic, lifestyle and environmental factors that would help to identify patients with high disease risks. The utility of this early identification (before the illnesses effects are suffered by the patient) is that it enables to take preventive steps for example lifestyle changes, early treatments and identification which enhances the likelihood of survival. The challenge of incorporating FHH information is the need for accessible collection methods, clinical guidance and health care provider access (Chan & Ginsburg, 2011).

Another essential tool to provide personalized medicine is a **standard health risk assessment** (HRA) to assess the odds of developing the most frequent chronic diseases such as the Framingham heart Study in which the chances of developing a coronary heart disease are estimated. The challenge of incorporating HRA studies in daily patient evaluation is due to a lack of infrastructure and standardization of these methods (Chan & Ginsburg, 2011).

To complement the use of FHH and HRA, **clinical decision support** provides both doctors and patients with person-specific information when is needed. The tools include alerts and reminders to care providers and patients, guidelines, patient reports and summaries, relevant reference data, diagnostic support, among other tools ("What is Clinical Decision Support (CDS)?", 2013; Chan & Ginsburg, 2011).

The main objective for researchers and policy makers is developing tests that will differentiate between responders and non-responders. To meet this priority, there are two business models that diagnostic companies are applying. The first and also nearer-term opportunity is the development of tests liked to existing therapies. Another possibility and also a longer-term opportunity is to link the tests with drugs

that are still under development. Diagnosis test and the drug will form a tandem to be commercialized together (Ferrara, 2007).

To sum up, human genome information allows physicians to predict risk, establish clinical diagnoses and direct clinical treatment personalized to each patient (Chan & Ginsburg, 2011). The techniques to provide customized healthcare and move from reactive to preventive healthcare do already exist; however, some main challenges need to be overcome if personalized medicine has to reach the mainstream.

Expiration date

Loss of potency is the main concern, mostly in antibiotics. Then should patients use expired medicines? It depends on the case. For example, medications that are essential for chronic diseases or life-threatening conditions is better to get a new prescription. However, for pills and capsules that do not comply with this requirements, is always better to get a new one but if the patient is not able to do so, he can take the medicine in most cases. But, if the patients experience a lower effect, change the medication (Anderson, 2014).

Big Data

Nevertheless, several challenges regarding data processing, analysis, data integration, interpretation and visualization need to be overcome in order to realize the full potential of big data in the field of healthcare (Panahiazar et al., 2014).

Data variety: To provide personalized medicine many different clinical and biological data has to be analyzed and integrated. The information is diverse in content but also in format as they are generated from different and heterogeneous sources. As most of the data is available in different formats, limiting its accessibility; thus, data needs to be more "understandable" and "interpretable". A possibility to solve this problem is the use of semantic web technologies which provide a common framework of sharing information in a more efficient way (Panahiazar et al., 2014; Cattell, Chilukuri and Levy., 2014).

Data Quality: By standardization of the way that data is collected and filed, quality of the information could be ensured and no differences between data sources would happen. A strategy is by establishing standard vocabularies which will make the data more understandable and easier to interpret for both agents and platforms (Panahiazar et al., 2014).

Data volume: having an enormous amount of data requires to summarize or abstract the meaningful data from the whole in order to use it to create personalized medicine. One useful tool is Hadoop systems which helps to process data in a faster way (Panahiazar et al., 2014).

Data speed: as healthcare is continuously creating and destroying data, these rapid changes need to be effectively captured by the data gathering system in real-time basis (Panahiazar et al., 2014).

What will Big data provide to personalized medicine?

- Patients are selected to participate in clinical trials based on doctors' visits, genetic and environmental data. This way, trials will be smaller, shorter, cheaper and more effective.

- Predictive modelling will enable to assess the drug effects faster and more effectively at the same time that a better understanding of biological processes will identify new potential-candidate molecules.
- Clinical trials will be monitored in real time to avoid adverse effects and delays.
- Data is integrated and available at all stages of drug development and testing and is shared between organizational functions.
- Portfolio decision support: big data will provide the tools to decide which assets to kill and which to pursue in a more effective and fast way.
- Data and data analytics will enhance the research of new drugs.
- Improve safety and risk management: analytical methods can identify adverse effects from the data introduced and improve the accuracy and speed of the detection (Cattell, Chilukuri and Levy., 2014).

PART B

Interview questions

3D printing experts

Expert opinion: Do you think drug 3D printing is a short-term reality or long-term? Or not a reality at all?

- **Drugs**
  - The current techniques enable the production of tablets; **would other products also be printed? (**in terms of 3D printing techniques**)**
  - How far is the research regarding drug 3D printing? (I mean the compounds that have been tested)

- **Requirements to make DRUG 3D PRINTING possible**
  - **Where is more likely to locate the printers**? Hospitals, pharmacies, production centers (so, manufacturing would remain similar to now) or in each patient's home?
  - **Are any complementary technologies needed**? (for example, 3D scanners, further development of material science, big data, etc.)

- **Challenges**
  - Technical requirements: speed printers, prices, etc.
    - **What are the technical requirements? Speed, ink?**
    - **How could high production volume be achieved? (**maybe the answer is that currently is not possible**)**
  - Regulation
  - Liability: **Who would be liable of the drugs printed if something happens?**
  - Copyright and patent: **How companies would protect drugs' formulation?**

- **Effects of drug 3D printing**
  - **Any effects? (**for example replacement of animal trials**)**
  - Supply chain (logistics): **How would the supply chain of pharmaceutical companies would change?** Pharmaceutical companies would supply compounds and printers? Only compounds and printers would be supplied by other sources?

Drug 3D printing experts

Drugs

- **What would the costs of the treatment be**? It would be more expensive I guess, so would companies and healthcare facilities invest in it?
- The current techniques enable the production of tablets; **would other products also be printed?**
- How far is the research regarding drug 3D printing? (I mean the compounds that have been tested)
- **Which known drugs could be 3D printed**? (has it been tested to produce ibuprofen for example? Or this is not applicable for mass products like this and drug 3D printing would be more for personalized medicine only?)
- **Expiration date**: immediately after printing or how to determine it?
- **What could be the production volume**?

- **Would it be possible the mass production**?
- **How could quality be ensured**?
- **How could dosage accuracy be guaranteed**?
- Would drug 3D printing completely change the current production paradigm? Or will it be complementary/ offering new opportunities?
- **How would the role of each stakeholder be?**
  - Physicians
  - pharmaceutical companies
  - patients
  - diagnostic companies
  - regulatory agencies
  - logistic companies

Requirements to make DRUG 3D PRINTING possible

- **Any change in company's organization**?
- **Where is more likely to locate the printers**? Hospitals, pharmacies, production centers (so, manufacturing would remain similar to now) or in each patient's home?
- **Are any complementary technologies needed**?

Challenges

- Regulation
  - What are the Standards needed?
  - How to ensure patients' Privacy?
- Liability: Who would be liable of the drugs printed if something happens?
- Copyright and patent: **How companies would protect drugs' formulation?**
- Technical requirements: speed printers, prices, etc.
  - **What are the technical requirements?**
  - **How could high production volume be achieved? (**maybe the answer is that currently is not possible**)**

Effects of drug 3D printing

- Supply chain (logistics): **How would the supply chain of pharmaceutical companies change? Would** Pharmaceutical companies supply compounds and printers? Only compounds and printers would be supplied by other sources?

Personalized medicine companies / experts

Drug personalization

- Which drugs can be personalized?
- Which illnesses are being researched/ are probable candidates to be personalized?
- Healthcare Costs that personalized medicine would cause: would it be cost-efficient?
- Reliability of the process? (the quality for example is the expected)
- Responsiveness of the production process? (process speed)
- Process efficiency?
- Liability: who will be liable for the drugs?

Requirements to make it possible

- Change in company's organization
- Supply chain (logistics): would it be changed?
- Production: Small batches or how?
- What would the strategy of the companies be? (existing versus new markets and new products versus existing)

Challenges:

- Regulation: standards
- Funding
- Research
- Education (doctors and patients)
- Train experts (sample collection and data analysis)

- **Drug 3D printing**: what do these pharmaceutical leaders think about it.
  - Do you think is possible?
  - Would it be cost-efficient?
  - Effects?

FOR PHYSICIANS:

- Where to locate the printer?
- Would it be feasible in the hospital? If yes, what infrastructure need to change?

Pharmaceutical companies

Company's position regarding drug personalization

- **What's your idea regarding drug personalization? (**only personalized treatments or also drugs like ibuprofen?**)**
- **How will you achieve it?** Smaller batches?
- **How can profits be maintained?** (different business model?)
- **Would the prices of the drugs be higher?**

3D printing of drugs

- **What do you think about it? Will it be a reality?**
- **What's your strategy regarding that**? (wait and see / check which drugs would be suitable for this/ active research or collaboration with partners).
- **What do you think will happen in the market**? (the first in the market will take all profits? Each company entering the market of drug 3D printing production will take a share? Anyone is ready yet to enter?
- **How would the role of each stakeholder** (physicians, pharmaceutical companies, patients, diagnostic companies, regulatory agencies, logistic companies) **change**?

Requirements to make Drug 3D printing/ personalized medicine possible

- Change in company's organization? (production organization or the structure of the company itself?)
- How could Supply chain (logistics) change? (your company will provide the formula and the requirements for us of that specific drug or would it provide the printer and the compounds too?)
- Expiration date?

Challenges that personalized medicine and/or drug 3D printing will face. What do you think about:

- Standardization of production
- Patenting and copyright
- Counterfeit drugs
- Train operators and physicians

Product-market combination: which of the 4 strategies would companies choose? (new/existing markets versus new/existing products): market penetration strategy, product development strategy, market development strategy or diversification strategy? *This question is more to know about what is these companies' strategy.*

Supply chain managers / researchers

- **Where will the 3D printing machine be located?** At each patient's home, hospitals, pharmacies?
- **What would be the production volume?**

- **What would be the consequences of this location and production volumes for the supply chain?**
- **What would the role of a pharmaceutical company be?** Provide compound formulation, raw materials for the printer?
- **What would the role of logistics be?** (if production is outsourced to customers their role would be more important than now or not?)

- **What need to change in logistics to enable drug 3D printing?** For example, warehouses will be reduced and production will be closer to the customer.

- **Last-mile transportation: how is it now and how would it change with drug 3D printing?**

- **How is the bargaining power of suppliers, pharmaceutical companies and logistic firms now and how would it change in the case of drug 3D printing?**

- **How can 3D printing…**
  - Increase connectivity inside SC
  - More flexibility
  - Increase visibility
  - Traceability of the products (avoid counterfeit drugs, ensure quality and good timing)

- Eliminate assembly lines

- **Key performance indicators**
  - How would **Responsiveness** be affected? Performance indicators are stock level, stock turns, cycle times, etc. (with 3D printing customer needs would be fitted)
  - How would **agility** be affected? (ability to accept external changes)
  - How would the **costs** be affected? (higher costs of production under drug 3D printing?) Would the price of medicines be higher?
  - How would **asset management** be affected?
    - Inventory no needed? Or just materials to produce the drugs and the printers?
    - Printers' production will be outsourced? Any change in the activities that are currently outsourced/ insourced?
    - Warehouse management, which problems does it have now and how it would be solved by drug 3D printing?
  - How would **supply chain efficiency** be guaranteed?

How would the pharmaceutical supply chain look like?

Regulatory experts

1. Do you think drug 3D printing is a short-term reality or long-term? Or not a reality at all?

The following questions will refer to a possible paradigm in which drugs could be 3D printed directly in pharmacies or in hospitals.

2. How would the current GMP practices change to "accept" drug 3D printing?

It comes to ask how the current regulations would adapt to produce drugs in hospitals and pharmacies instead of producing them in a controlled environment like a manufacturing facility.

3. How a change in GMP affect pharmaceutical companies?

4. What would be required to ensure quality and reproducibility of drug production?

5. What are the necessary standards?

Some experts of drug 3D printing have pointed the need of establishing standards regarding materials used and printers.

6. How counterfeit drugs could be avoided?

A big challenge of drug 3D printing is the possibility of produce fake copies of the medicines. Do you have any idea of how to avoid that?

7. How labeling and packaging would change?

If personalized medicine is produced by 3D printing, each patient will get his or her own medication, then, how packaging will change? And will they require any different labeling to control in which machine and by whom have the medicine been printed?

8. Any changes in quality testing?

9. Will the FDA regulate the 3D printer or the end product?

10. In the case of 3D printed medical instruments, they could be considered as "custom devices" so they are exempt from per market approval requirements and mandatory standards. Could that happen with drugs?

11. How will FDA programs get affected with this new technology to assurance QS and GMPs requirements?

Interview transcripts

3D printing experts

Dr. Tobias d. Gantner (3DM conference contact)

Tobias D. Gantner works at HealthCare Futurists GmbH specialized on 3D printed dispensers which dispense data on patient's physical conditions and that can also be implanted in the patient's body. He was a speaker at the 3D Medicines Printing Conference held on January 27th, 2016 in Maastricht, The Netherlands about "Imprintables: A new class of products empowering patients, physicians and consumers alike." Imprintables are suited for diseases such as cardiac defibrillators or for contraceptive use.

Source: http://www.3Dmpconference.com/pharmaceuticals/tobias-d-gantner-md-mba-ll-m-healthcare-futurists-gmbh-will-speak-at-the-3D-medicines-printing-conference-on-imprintables-a-new-class-of-products-empowering-patients-physicians-and/

Do you think drug 3D printing is a short-term reality or long-term? Or not a reality at all?

It is a hot topic right now in a number of labs. Will it be marketed? We don't know.

- Drugs

- **Personalized treatment or high volume: What type of drugs are more likely printed? The ones that can be personalized or a normal aspirin too?**

I would think we are looking at generic drugs in the first place.

- **What would the costs of the treatment be? It would be more expensive I guess, so would companies and healthcare facilities invest in it?**

It depends on the economy of scale and the location. Where will drugs be printed? @home, @the pharmacy @the hospital?

- **The current techniques enable the production of tablets; would other products also be printed?**

NO ANSWER

- **How far is the research regarding drug 3D printing? (I mean the compounds that have been tested)**

Consult the official company webpages to see what its public domain is.

- **Which known drugs could be 3D printed? (if 3D printing would be used for new personalized drugs, this question is not applicable anymore)**

NO ANSWER

- **Expiration date: immediately after printing or how to determine it?**

Open question along the lines with regulatory requests. Needs debate and will be different from country to country.

- **Would drug 3D printing completely change the current production paradigm? Or will it be complementary/ offering new opportunities?**

I think it will be complementary as much as I can foresee it. But it will most likely also depend on the geographic location and the logistics involved.

- **How would the role of each stakeholder (physicians, pharmaceutical companies, patients, diagnostic companies, regulatory agencies, logistic companies) change?**

Hard to say. Very much correlated to the question above as where drugs will be printed.

Requirements to make DRUG 3D PRINTING possible

- **Where is more likely to locate the printers? Hospitals, pharmacies, production centers (so, manufacturing would remain similar to now) or in each patient's home?**

No definite answer possible as of today. I would say in the first wave it is pharmacies and hospitals.

- **Are any complementary technologies needed? (for example, 3D scanners, further development of material science, big data, etc.)**

NO ANSWER

Challenges

- **Regulation**
- What are the Standards needed?
- Prevent counterfeit drugs

- Privacy (patient information)

- **Liability: Who would be liable of the drugs printed if something happens?**

NO ANSWER

- **Copyright and patent: How companies would protect drugs' formulation?**

NO ANSWER

- **How could high production volume be achieved? The question is: is it needed? Why?**

I guess we are much more looking at customization in the first place and then heading towards mass customization.

Mr. Robert Palazzolo (LinkedIn contact through group 3D printing)

Development Engineer at Terumo Cardiovascular Systems who did his master thesis on oral dosage forms by 3D printing in 1997.

I view the main challenges being

1. DEMONSTRATING AND MAINTAINING A CLEAN ENVIRONMENT
2. DOSING ACCURACY
3. REPEATABILITY
4. VALIDATION will be key, as with any pharmaceutical process.

Additive manufacturing has advantages for **drug stability and control** options. The operation is software-based, so it is very easy to make adjustments, which is often time consuming and expensive. The disadvantage is **throughput**, although scale-up can be done by adding more machines. At the same time, ease of **scale-up** makes bringing from R&D to **production easier**.

Dr. Pedro Costa (secondary contact)

Pedro Costa is a Postdoctoral Researcher who works at the Utrecht bio fabrication Facility & Department of Orthopedics. A part from that, he is the Coordinator of the Bio fabrication MSc Program at Utrecht University and the manager of the Utrecht Bio fabrication Facility.

Drugs

- **Personalized treatment or high volume: What type of drugs are more likely printed? The ones that can be personalized or a normal aspirin too?**

Personalized ones since those are the ones that cannot be easily produced through standard (highly efficient) mass production industrial processes.

- **What would the costs of the treatment be?**

It would be more expensive when compared to standard mass production, however personalized medicine could be a large part of the market in the future since it allows in fact a more efficient treatment, therefore, overall the cost of healthcare would be reduced.

- **The current techniques enable the production of tablets; would other products also be printed?**

The great thing about 3D printing is that it allows to create objects with any shape, size or architecture. Even within just tablets, they can be produced in different sizes, shapes and architectures (i.e. tablets with specific porous structures which would possess a tailored drug release behavior over time). This principle can be applied not only to tablets but as well to other medical products. As an example, it can be applied to implants which have incorporated drugs which, after implantation, are released in a certain tailored fashion over time.

- **How far is the research regarding drug 3D printing?**

  In attachment a review about this.

Article: Jonathan, G., & Karim, A. (2016). 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. International journal of pharmaceutics, 499(1), 376-394.

- **Which known drugs could be 3D printed?**

  The attached review can answer this question.

Article: Jonathan, G., & Karim, A. (2016). 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. International journal of pharmaceutics, 499(1), 376-394.

- **Expiration date: how to determine it?**

  The expiration date would be the same as in normal medication since it is mostly based on how long the drug's active principle lasts.

- **Would drug 3D printing completely change the current production paradigm? Or will it be complementary/ offering new opportunities?**

  It will be an important complementary option addressing an important part of the market but not completely replace what exists.

- **How would the role of each stakeholder change?**

Physicians will prescribe more specific treatments, patients will have a better treatment, companies will (apart from the standard drug formats) offer precision dispensing devices (3D printers) which will generate treatment-specific tablets (or other forms), logistics will involve as well delivery of bulk drugs which can be loaded into the 3D printers, regulatory agencies will also regulate drug 3D printers.

<u>Requirements to make DRUG 3D PRINTING possible</u>

- **Any change in company's organization?**

  New additional divisions (apart from the existing ones) specialized in 3D printed drugs.

- **Where is more likely to locate the printers?**

  Hospitals and pharmacies

- **Are any complementary technologies needed?**

New advanced materials for improved delivery of drugs
Software for generation and management of the 3D printed medication

Challenges

In general, I believe that most of the rules/regulations/policies established for standard medication could be applied to 3D printed medication (with some minor modifications).

- **Copyright and patent: How companies would protect drugs' formulation?**

Apart from the active principle (which is what usually is patented and will still be possible to patent and protect) formulations will be difficult to protect.

Technical requirements

- **What are the technical requirements?**

Fast printers based on mild processing conditions (mild temperatures/solvents)

- **How could high production volume be achieved?**

By applying distributed production/manufacturing (printers in all hospitals and pharmacies)

Effects of drug 3D printing

- **Supply chain (logistics): How would the supply chain of pharmaceutical companies change?**

I believe that this will be taken over by pharmaceutical companies which will sell/supply the printers and their "drug inks/materials"

- **Any other effects?**

3D printing is in fact in the process of changing drug trials since it allows 1-generate more realistic bio printed tissue models and 2-easy generation of high throughput tests

Expert opinion: Do you think is a short-term reality or long-term? Or not a reality at all?

It will definitely be a reality. Maybe medium-term, but of course will depend on how quickly and actively the stakeholders will adopt this technology.

Drug 3D printing experts

Mr. Erkan Azizoğlu (LinkedIn contact)

Visiting Scholar at the Laboratory of Drug Delivery, Georgia Institute of technology. He is working on the development of formulations and fabrication methods for drug loaded micro needles. Both master and bachelor were at the Pharmacy faculty in Ege University, Bornoa, Turkey. He has been researching drug 3D printing for couple of years.

Drugs

- Personalized treatment or high volume: What type of drugs are more likely to be printed? The ones that can be personalized or a normal aspirin too?

I guess it would be mostly personalized treatment. It cannot reach the speed of the production of standard tablets like aspirin.

- What would the costs of the treatment be?

Well that depends. It would be much more expensive to make personalized treatment (different doses, coatings, release profiles etc.) for each patient.

- The current techniques enable the production of tablets; would other products also be printed?

Sure, for example implants, patches, suppositories, ocular inserts…

- How far is the research regarding drug 3D printing?

Too many… But doable…

- Which known drugs could be 3D printed?

With common filaments, the drugs should have heat resistance and the polymers for printing should not be interacting with the drug for chemical stability.

- Expiration date: immediately after printing or how to determine it?

Short/long term **stability studies** should be made. But I guess it will be long term since the product will be in solid form which is good for stability.

- Would drug 3D printing completely change the current production paradigm? Or will it be complementary/ offering new opportunities?

I would say complementary and new opportunities, but I think it is a new area which should not be compared conventional production methods. I mean; it's not changing the current ways; it's adding new ones.

- How would the role of each stakeholder (physicians, pharmaceutical companies, patients, diagnostic companies, regulatory agencies, logistic companies) change?

Pharmacists (me too) were already making personalized treatments for each patient. With 3D printers that will have new dimensions. For example, you can make one tablet with different drugs, so a pharmacist can make combined drug formulations for each patient with their needs. So they won't have to take lots of tablets at a time. That's just a basic example. With this example I can say that, pharmaceutical companies will make filaments instead of tablets with many different doses (cost effective) logistic companies will carry smaller things, just filaments of the drugs, not individually packaged tablets (cost effective). In the case of diagnostic companies, their role would be similar than now with pharmaceuticals. And regulatory agencies will have the hardest work as the tablets will be made everywhere instead of a few factories.

Requirements to make DRUG 3D PRINTING possible

- **Any change in company's organization**?

Well probably all of them are making filaments somehow, instead of breaking them into pellets or granules they can sell them directly.

- Where **is more likely to locate the printers**?

Not patient's home. 3D printers can be used like a toy but drugs cannot, so most likely they will be printed in pharmacies or hospitals.

- Are any complementary technologies needed?

Packaging of course. Sterilization if needed. Most important thing, new materials. You cannot use PLA for everything (for FDM). New biocompatible polymers needed.

Challenges

Regulation

- What are the Standards needed?

Standard materials, like filaments with drugs and also **standard printers**. They have to make the same product every time, so to ensure quality and reproducibility.

- How would it be possible to prevent counterfeit drugs?

I think that is not relevant with 3D printers. That is another topic.

- How to ensure patients' **Privacy?**

That is not about 3D printers too… Recipe comes to pharmacy, pharmacist makes the drug, that's it like always been.

- Liability: Who would be liable of the drugs printed if something happens?

  Pharmacist. I suppose that the filaments were tested and has the same quality every time (like other drugs comes to pharmacy). And if the printer in a pharmacy works well (like other devices) the only thing that may cause a problem will be the user. And the user should be a pharmacist.

- Copyright and patent: H**ow companies would protect drugs' formulation?**

  Like they always do.

Technical requirements: speed printers, prices, etc.

- What are the technical requirements?

Well speed is OK if you are making a something like a tablet. Prices are OK too. But new materials is a very sensible topic and also the most important.

- How could high production volume be achieved?

That is not impossible. It would be like a cupcake production line, with many nozzles printing at the same time… (But that would be for a specific product, not a personalized one)

Effects of drug 3D printing

- Supply chain (logistics): How would the supply chain of pharmaceutical companies change? Would Pharmaceutical companies supply compounds and printers?

Approved printers can be supplied by other sources too. But the product for the drug should be supplied only by pharmaceutical companies.

- Any other effects? (for example replacement of animal trials)

I don't see anything about animal trials. The most important thing will be about the life quality of the patients I think.

Dr. Clive Roberts (3DM conference)

Head of School Laboratory of Biophysics and Surface Analysis, School of Pharmacy at the University of Nottingham. Dr. Roberts has an internationally leading reputation in surface analysis of pharmaceuticals, polymers and biomaterials; he has received some international awards such as the GlaxoSmithKline International Achievement Award in 2003. His current research focused on the development of new medicines by the application of innovative analytical and formulation strategies. More specifically, his line of work is in the area of printing solid dosage forms.

Source: https://www.nottingham.ac.uk/pharmacy/people/clive.roberts

- What do you mean with "**manufacturing models**" in your presentation for 3D medicine printing conference in Maastricht?

It is about the fact that 3D printing opens the possibilities for distributed manufacturing. In the industry it has been discussed the possibility of having a factory somewhere in Africa. So, it frees out the supply chain in terms of manufacturing. The other interest is having the manufacturing site in a hospital with 3D printing. In this case, the pharmaceutical industry will be delivering the inks and the distribution will be closer to the customer/ patient. You can go further and have a printer in pharmacies and also, in the future, even at homes. This raises regulatory concerns but it's interesting to analyze what would happen: changes the current manufacturing model that consist in big manufacturing plants completely regulated.

But, of course, that is not going to happen with all medicines. And it opens the opportunity for distributed manufacturing but not necessary has to be this; APRECIA pharmaceuticals model is still centralized but with 3D printers as a manufacturing system.

At the moment, in the department we have engineers and management people assessing the economic analysis of the new supply chains that 3D printing could bring. The issue is that because the technology is moving so quickly, the numbers change continuously.

- What's your opinion about: "**regulators don't like polypills**"

As an academic is an interesting exercise to demonstrate that it is possible to make. The regulators are "against them" because now the western regulatory framework apply just to pills with 1 single API so no interactions between components, etc. what means is that the regulatory framework cannot deal with them is not that isn't interesting clinically.

Is the same problem that happened with traditional medicine that were combination of different herbs. So, I completely agree that under the current regulatory framework are not likely to be popularly manufactured. Is because they do not fit. But, as always, regulations can change. Nevertheless, if it happens would be in the future.

The papers demonstrate the flexibility of 3D printing. The possibility to have various APIs in the same pill is something that was not achievable with the current medicine system. Thus, 3D printing medicines have more possibilities in fields where regulations are less strict such as cancer or neglected diseases because the need is great. I agree with the statement: "in regulators' world is not likely, it could be but it requires

more work because it could be that a patient has an adverse reaction to one of the components inside the pill; so in the clinical point of view it may have more sense to produce pills separately". The more drugs that you combine, the more possibilities to experience side effects.

- What do you think about **dosing accuracy**?

First, depends on the printer that you are using. In broad terms, I don't see this being a problem. Because if you see the ability of control in printers, as long as the ink is correct, the accuracy that 3D printers have now is more than enough to print pharmaceuticals even in low dosages. The tricky part is to have an ink that is reliable and stable. If you have a printer in the hospital, it could be very simple to have a quality control check point that ensures the quality of the printed pills. **In current technologies, this is no longer an issue.**

- And about **production volume**?

This is the question everyone asks everyone thinks about 3D printing in the old fashion way: printing prototypes. However, being said that, if you think about having a printer at home it doesn't matter how much it does take to print a tablet. In our laboratory, that is a research based printing not production, we can have a tablet printed and dry in about 1 minute. And it is still quite slow, one tablet per minute if you compare with the current production systems.

Speeds are increasing rapidly, so the limits are the inks not the technology. The current research is focusing in the inks not the printers. In terms of printing in hospitals, I believe that we can easily think in terms of **1000 of tablets/day**. But the question to ask is: "is there a clinical requirement for this type of medicine and what is the volume required?". The answer to that question would be quite a lot, but the essential is to **find the clinical need.** In the case of APRECIA what they found was a clinical need to fulfill and coming up with the manufacturing technique to do so.

Although, there's a big uncertainty here because the pharmaceutical industry is very slow accepting new technologies. This is because of the high risk involved in product failure or withdraw: will the patients accept it, will the regulators do as well? In this industry is not the technology that wins, is the commercial step later. What matters is not the clinical success, is more the commercial success later on.

Getting an FDA approval is not that difficult, the only things that need to prove are quality and safety. They do not care about the business model, if it is good or not. There's a case of Pfizer that produced a new method to administer insulin by inhaling. The product got FDA approval but it was not convenient to use, people didn't like it. So, although it was a very interesting clinical product, it was a disaster commercially. In the case of APRECIA, if it fails, it won't get back. Is all about the confidence in this field, the food market is far easier however is a low value product with enormous scales and low margins.

Other industries are making commitments in the field of 3D printing, for example in the plane business, GE made the commitment to print out 20 to 30% of their components by 2025. However, in the pharmaceutical field everything is more conservative because it is not solving an existing problem or something missing in that field.

- What is going to be **the role of each actor** involved in the pharmaceutical supply chain with the adoption of 3D printing?

In the distributed model, what makes sense is to have a file with the formulation and selling the inks (is where the value is located). But if it is still centralized, anything would change.

- Pharmaceutical companies adopting this new production model:
    - **Production strategy**: combination with current methods or completely new paradigm?

Combination of methods most likely in the mid-term.

- **Inkjet and extrusion printers: which is the most suited for drug 3D printing.**

Most of the current fabrications are done by **extrusion printers** there are some exceptions**. Extrusion** is a very familiar process for the pharmaceutical industry. Is a very well understood process. That also means that all the used materials are already known, so approved for manufacturing. So there's nothing to worry. Also, the technique is simple and fast.

Inkjet is interesting because it gives the opportunity to make more complicated structures and compositions with high resolution and has the potential to be quicker. The problem is to make the medicines reliable and fast, at the moment, they need materials that are not approved and definitely toxic. Ultimately it's very interesting but at the moment is not happening.

There are other ways to produce 3D printers like **fuse filament deposition.** It is similar to extrusion but the ink is a solid wire instead and it is melted to give a shape.

- Why apart from Aprecia pharmaceuticals anyone is in the mass market?

No idea.

- TEVA pharmaceuticals put emphasis on the fact that APRECIA's business idea is not enough for pharmaceutical companies to move onto this new manufacturing model. What do you think?

It has to see its commercial success, if customers accept it, etc.

- What would the **regulatory requirements** be?

They will require the same standards that another manufacturing tool: GMP mainly. However, is not that hard to get approval for the manufacturing method. If you are producing a simple tablet without much complications, regulators will not really care how it is made as long as the quality, safety and stability is the required.

- **Ideas about the industry (AstraZeneca or GSK**)
    - **What is their position regarding this technology?**

I can say that every single pharmaceutical company is seriously considering it (huge investments are going on)**.** Their concern about is to see the potential competitive advantage that this brings.

- **What is their idea about personalized medicine? Are they investing in it**?

Personalized medicine is slightly different because it is an area that is already developing. If you talk about a drug that can be made with different dosages and for different people, that is where 3D printing has a chance. But if you are talking about continuous dosage variation is a long way to achieve it. But that is not that common.

- **Pharmaceutical supply chain**: how will it change? (last mile transportation)

This is not my area of expertise but they will be distributing high quality materials in their final form. With 3D printing, there will be many different cartridges. That involves less transportation but the quality change would need to be moved all way through the supply chain. Now each batch is quality checked, how that would be in the distributed manufacturing model is an open question.

It's worth remembering that in most parts of the world, pharmacists can produce medicines themselves to personalize them. What would the change with 3D printing then? Also, in many parts of the world, this is currently the way medicines are produced and we forget that there would be big chances there for 3D printing. It's interesting to bear in mind that all what we talk about regards the western world.

Supply chain managers/ experts

Dr. Samuel Roscoe (internet)

Dr. Roscoe is a Lecturer in Operations Management at Sussex University and teaches in the areas of Operations and Supply Chain Management. He completed his PhD at Manchester Business School in sustainability. He organized the conference "*The Future of Pharmaceutical Supply Chains"* held last 3th of March 2016 in Brighton, United Kingdom. Currently researching on Drug 3D printing and the way it would affect the supply chain in the UK.

Sources: http://www.sussex.ac.uk/profiles/163978

https://www.eventbrite.co.uk/e/the-future-of-pharmaceutical-supply-chains-tickets-20923076485?ref=enivtefor001&invite=OTA2NTU2My9kaGFybS5rYXBsZXRpYUB1d2UuYWMudWsvMA%3D%3D&utm_source=eb_email&utm_medium=email&utm_campaign=inviteformalv2&ref=enivtefor001&utm_term=attend

INTERVIEW

- **What do you think about the role of 3D printing in the future of Supply chains?**

3D printing also called re distributed manufacturing, which is manufacturing in local markets for local customers; the whole idea is to **reduce supply chain risks**. By producing in local markets, the supply chain is reduced and that would cause a reduction of the risks like disruptions and delays in the supply chain in addition of lower inventory levels. Holding inventory is the main risk because it is hold during from 3 to 6 months in multiple nodes of the supply chain (raw materials, GSK or Pfizer manufacturing facilities, secondary warehouses, etc.). So, lowering inventory and shortening the supply chain would lower the costs of these companies. The other risks are the ones that come along with globalized supply chains such

as natural disasters, wars, political situations, infrastructure issues, transport issues, etc. As well as IT risks and forecast risks.

- **And in the case of drug 3D printing in pharmaceutical supply chains?**

The benefits of drug 3D printing are obvious, but what I am trying to understand is why large pharmaceutical companies are not adopting this technology. A part of the obvious that are the risks involved in innovations and adopting new technologies, there's no take up of 3D printing in the pharmaceutical industries at the moment. The companies have adopted a **wait and see strategy**. This is curious given the fact that 3D printing has gained recently a big ground in aerospace and medical implants fields. However, in products like pills they are not adopting it. The main reason for that is the high level of investment and sunk costs in infrastructure (GSK, Pfizer) to obtain the actual centralized production model. Currently they have the ability to produce drugs cheaply specially generics; so, **moving towards additive manufacturing and re distributed manufacturing doesn't make sense for them at the moment**. The main reason follows the **cost argument:** very expensive technology, can't produce in the large scale, not enough machines at a low price, not enough expertise of how to use it and regulatory challenges that haven't been overcome yet. And these are the difficulties in terms of adoption.

- **Where will the 3D printing machine be located?** At each patient's home, hospitals, pharmacies?

The machine will be located where it adds more value in the supply chain. For me, is more of understanding what 3D printing good is for. Again I think it will never be used for the production of tablets or generics, it will be more to manufacture **niche products and specific markets** (consumer groups with specific requirements or preferences). Most likely it would be at the point of use when it's needed. That's what the technology needs to be proven. So that's where 3D printing has options that is in the field of personalized medicine. The idea that the experts in the field are suggesting is the possibility of **putting 4-5 different formulations and combining into one**. But the industry experts say that it's incredibly difficult because it's hard to understand how those drugs interact when they are together and get regulatory approval for that. That they don't think that this is actually viable. Additive manufacture can actually do it but doing it on large scale with regulatory approval is not happening in the near future. And my work consists in finding which these applications are. In the UK market big pharmaceutical companies aren't rushing out to pick up this technology. It's more likely to happen in hospitals or even pharmacies but it has to be for a very specific usage.

A company called Aprecia pharmaceuticals have already produced 3D printed drugs with high dosages and that are absorbed really fast. But, again, the costs would be exorbitant. Possibly the main reason why the technology is not being adopted is because the proper use hasn't been identified yet.

Personalized medicine: high end therapies and genetic drugs which it could be a potential area but is very sophisticated and is not working in the normal basis (current manufacturing modes) so is not likely to work with 3D printing; at least not in the upcoming 10-20 years.

There's a lot of excitement around what 3D printing offers to the de centralized manufacturing models and drug production but when you talk to the industry, they are very reluctant to it. For the regulatory and cost challenges doesn't make sense right now.

- **How would it affect the supply chain?**

There's an idea of applying to the pharmaceutical field the **amazon model** where there's a large distributor that sells directly to the patients' door. The idea is like generics that don't require unique prescription, which you can buy them directly on the internet.

The problem is that currently pharmaceutical companies sell to the reseller that are responsible for the final mile delivery. So, in the case of Merck, Pfizer and GSK they sell to another distributor and that to the pharmacy. So you have 1 or 2 additional steps in the supply chain that is a bit redundant. This has potential as well.

Then, who has the patent is the one that is in charge of providing the information to the pharmaceutical company. So, the supply chain would be aligned to who has the patent or the ownership of it.

Scale/scope change? (Number of customers, domain breadth, customer products and product line**)**

- **What would the strategy for companies be?**

I don't think that Aprecia would lower enough the costs to deliver to the mass market at least with the technology that they have right now. If Aprecia can prove that the technology works, the big pharmaceutical companies will buy them out.

- **What need to change in logistics to enable drug 3D printing?** For example, warehouses will be reduced and production will be closer to the customer.

Pharmaceutical companies would buy the 3D printers and raw materials to their suppliers. Specialized suppliers would produce the 3D printers; I don't think that companies like GSK would develop 3D printing machines in their facilities. The suppliers would keep ownership on 3D printers and raw materials because is there where they have their competitive advantage (the technology and expertise would be controlled by them). This is the most likely alternative. There are already small 3D printing companies that are considering this alternative, at least in the UK.

- **Key performance indicators**
    - How would **Responsiveness** be affected? Performance indicators are stock level, stock turns, cycle times, etc. (with 3D printing customer needs would be fitted)

Responsiveness would be higher as the production would target customers' needs.

    - How would **agility** be affected? (ability to accept external changes)

Obviously, if you could afford a big number of 3D printers that could produce these medicines very quickly, you would have an incredible agile supply chain, you could shorten your **lead times in the supply chain** by months and years. So you would have a huge benefit there but this is a very far alternative. If you are

manufacturing in a local market for local customers, you would have a **huge competitive advantage in terms of speed and flexibility.**

- **Supplier power**

In vaccines for example, they have a lot of single sourcing arrangements with primary manufacturing (those are the producers of API and antibodies) and those arrangements there are large suppliers like GSK that has a lot of power in that relationship; the supplier has a balanced power in the relationship in the sourcing arrangement. The difficulty that that creates is if something bad happens, as all the regulations are attached to that supplier, it's difficult to change them. With 3D printing you wouldn't have that issue.

- **How would the costs be affected**? (Higher costs of production under drug 3D printing production?**) Would the price of medicines be higher?**

The costs would be highly increased; that's why it only makes sense for the case of very personalized products and not for large non customized products like ibuprofen or generic medicines.

- How would **asset management** be affected?
  - Inventory no needed? Or just materials to produce the drugs and the printers?

At the **Decoupling point** we keep the raw materials close to manufacture and we don't actually make any product until you have an order giving a lot of flexibility. Thus, orders are based on forecasts, but those are not always correct (over supply or under supply). If you produce directly as soon as you have an order, you will cut your inventory costs significantly. This is in an ideal world where you have enough capacity to adapt to the current demand.

  - **Printers' production will be outsourced? Any change in the activities that are currently outsourced/ insourced?**

Already answered.

- How would **supply chain efficiency** be guaranteed?
- **How can liability be ensured?**

It's not clear who would be held responsible if something goes wrong.

In **counterfeiting,** there's an ability to 3D print on them a barcode. So this gives you the ability to track each pill not just the package itself. This would solve a big problem that physicians have with patients. A big issue in the pharmaceutical industry is that patients don't take what they have actually prescribed. In terms of counterfeiting, the product would be track in each of the stages of the supply chain.

Another option is to apply barcode 3D printing into normal pills.

- **How quality will be ensured?**

Most pharmaceutical products are produced in batches, so to ensure quality, in quality control you tied back to the batch itself. In the case of 3D printing, it's not in batches, it would be in an ongoing flow. This is linked with regulation.

Final thought: before this centralized system changes, there's going to be decades. Too much cost involved and too many people with interests. So the model would most likely be that the big pharmaceutical companies would adopt 3D printing as a production system of very personalized medicines for a niche market. It would be a parallel production system.

Dr. X

Assistant Professor in Additive Manufacturing Management, Faculty of Engineering of the University of Nottingham, UK. Already in his master dissertation he was interested in 3D printing and Additive manufacturing and after completing his PhD, he has managed the research group of Additive Manufacturing and 3D printing at Nottingham University. His focus are the economics and efficient operation of Additive manufacturing and the benefits of adopting this technology (source: https://www.nottingham.ac.uk).

In his article "*The cost of additive manufacturing: machine productivity, economies of scale and technology-push*" he points out that while experts in the manufacturing sector and AM point that AM will have a deep economic impact on the manufacturing sector and in the society, its high costs and low deposition rates are the main challenges to widespread this technology. However, it also points out the possibility of achieving economies of scale. By increasing the system productivity, the operating costs of AD will decrease and thus, support high-volume manufacture.

Regarding economies of scale, these are defined as situations in which the companies can decrease the average unit costs when the total output is also increased. In the conventional manufacturing processes, economies of scale are achieved by amortizing tooling expenses. However, as AM do not use tooling (apart from the 3D printer itself), the importance of economies of scale would decrease and enable the decentralization of production to points of consumption. Furthermore, AM processes target an increase of productivity by no stopping the production process or by depositing build material on multiple layers at the same time.

To achieve economies of scale with AM, the idea is to increase machine throughput or scaling them up. Economies of scale are essential for the diffusion of 3D printing into applications produced by industries characterized by high fixed costs.

Source: Baumers, M., Dickens, P., Tuck, C., & Hague, R. (2016). **The cost of additive manufacturing: machine productivity, economies of scale and technology-push.** Technological Forecasting and Social Change, 102, 193-201.

INTERVIEW

- **Where will the 3D printing machine be located to be as cost effective as possible?** At each patient's home, hospitals, pharmacies?

I recommend you to read the article: *"3D opportunity and the digital thread"* were 3D opportunities are discussed in a nice and methodological way how supply chain should be chosen and the reasons for that. The logic behind is that so far is pretty unclear whether distributed manufacturing configuration is the right configuration for 3D printing or not. They say that will depend on the business setting and strategy

and that I completely support. And that would apply of course into the medical field as well. So in order to answer what would be the opportunities or consequences of 3D printing in manufacturing, the correct way to approach this is to start asking ourselves what is the business strategy and what makes sense in terms of ownership structure and so on.

To make it short, I think is currently unclear where these machines will be located and will depend very much on the product, the strategy of the company, customer's benefits. Because we know so little about how this would look like in the future, is important to apply so sort of methodology to understand what the variables are and to basically answer this open question in which there are many stakeholders in the process with many different opinions and interests.

In the article *"3D opportunity and the digital thread",* argues that to move 3D printed objects into the mainstream, a series of data-driven events need to happen to enable this transition. The series of data-driven events is referred as the *digital thread* where the same strand of data is used from the early design to the final production of the product and it helps to design, model, produce, use and monitor the 3D manufactured part. In this way, the data is used to design the product, ensure quality and also for the post-production inspection and monitoring. So, to move AM from prototyping to mass production is essential to establish this digital thread, the amount of data necessary and the infrastructure required to store, access and analyze all this data.

Source: Cotteleer, M.,Trouton, S., & Dobner, E., (2016). 3D opportunity and the digital thread, *Deloitte,* Retrieved on 13 April 2016 from http://dupress.com/articles/3D-printing-digital-thread-in-manufacturing/?coll=8717 .

- **How can drug 3D printing (and additive manufacturing) be cost-efficient?**

In this field I recommend that you talk to some people or companies that know exactly how this technology operates. If you talk to these people they will tell you that in principle machine productivity is important but, on the other hand, there's a high degree of variation in the additive manufacturing processes. And in an application like in the medical field, robustness and predictively is essential. Actually, this is very difficult because in many processes this doesn't exist yet. I would argue that, ignoring machine productivity and costs, process controllability and reliability are the main challenges to overcome if drug 3D printing is going to be a reality. Also, there are many non-technological barriers to apply this technology in the medical industry: liability questions, regulatory questions that haven't been answered, IP, etc.

A very interesting thing in the pharmaceutical field is that per unit revenues are pretty high in comparison with other industries. And this gives them more flexibility in technology choice.

In the medical area and dental applications are more frequently that in the drug field because the strategy is completely different: there's a phenomenon of **technical substitution** going on in which the current production procedure is being changed for a one with lower labour costs. In the dosage forms this relationship does not really happen because there's no shift from traditional and more manual manufacturing to a more automatized, the procedure is already automatic and dynamic.

- **What would be the production volume?**

To be honest, I have no idea. Mainly because the time horizon of this technology, currently high volumes cannot be achieved but in a future horizon with technical advances that make this production more specific for drug production, it would be more likely to achieve high manufacturing volumes.

Area of economics of scale: there are people that say that there are economics of scale whereas others say that not, so this is a very interesting field to look into. I personally believe that there actually economics of scale. It will depend on the technology, the investments that are already made, strategies of big players, etc.

- **What would be the consequences of this location and production volumes for the supply chain?**

No idea.

- **What would the benefits in the supply chain / pharmaceutical companies be for the use of additive manufacturing?**

There are two main benefits:

- Geometry freedom: control shape and geometry and composition (properties). With this ability you could make very complex products for example pills that dissolve faster or mixture of ingredients, etc. **Improve product functionality**.
- Customizing: everything is design driven so we can easily change stuff as well. Different dosage to each patient, etc. so there are no more **product barriers.**

I believe that both of them apply in the pharmaceutical field.

In the sense of supply chain, the degree of distribution will depend on the business strategy so it's particularly unclear and only answerable later on. With the term degree of distribution, I want to say that between completely centralized and de centralized (where each patient gets its own medicine), there's a big space that separate them, so there are many in between strategies that companies can choose. In principle, in terms of logistic expenses it's a thing that should be avoided. A very useful question to ask is *whether the benefits of centralized manufacturing large enough to justify a more distributed setting*.

- **What would the role of a pharmaceutical company be?** Provide compound formulation, raw materials for the printer?

They will adopt a role that maintain their competitive strengths that they have at the moment. So I would be very surprised if they move from manufacturing the APIs. So, they won't compromise their actual business model. Whether they will own the printers or not is more a secondary question.

- **What would the role of logistics be?** (If production is outsourced to customers their role would be more important than now or not?)

It would depend on what business advice would be beneficial and the strategy. It's completely unclear.

- **What need to change in logistics to enable drug 3D printing?** For example, warehouses will be reduced and production will be closer to the customer.

Depends on the strategy as well.

- **How is the bargaining power of suppliers, pharmaceutical companies and logistic firms now and how would it change in the case of drug 3D printing?**

Pharmaceutical companies are very profitable and as far as I understand, their strategy consist in absorbing the risks of developing APIs. As soon as they manage to get a large volume medication approved, they obtain big monopoly profits. So, I guess they will adapt their strategy to continue achieving these profits by retaining IP and production. I don't think they care that much about trying new manufacturing techniques.

- **How can 3D printing…**
    - More flexibility

Flexibility is demonstrated as long as there's patient benefits in customization and there's a way of making money with it.

    - **Increase visibility**

In principle, AM is characterized by very short supply chains because the deposition of the material happens basically in a single process so then, there's an opportunity to gain transparency in this process. So this is the main advantage of this new technology. It becomes very clear what is happening and also very transparent as all is digitally controlled (obtain records, data).

    - **Traceability of the products** (avoid counterfeit drugs, ensure quality and good timing)

It is easy to generate data about what's going on in the manufacturing process (short, consolidated and localized process).

    - **Eliminate assembly lines**

It eliminates assembly lines because, as previously mentioned, all the production happens in one step, only one material deposition.

- **Key performance indicators**
    - How would **Responsiveness** be affected? Performance indicators are stock level, stock turns, cycle times, etc. (with 3D printing customer needs would be fitted)

Unclear.

    - How would **agility** be affected? (ability to accept external changes)

Unclear.

    - How would the **costs** be affected? (Higher costs of production under drug 3D printing?)

A very good question, depends on the industry, the appetite for this technology and also in its profitability. I would start asking questions like, how large the manufacturing costs are from the total costs. This is an important question because if this share is really small, they will not care that much about those costs; but if they are really big, it's a big deal. In my impression, their production's costs share is relatively small so, they are not very sensitive in this terms. Then, they can still be interested in new production processes regarding company strategy or innovation, but not under the idea of lowering the production costs.

I don't think there's a cost driver in the adoption of drug 3D printing.

- How would **supply chain efficiency** be guaranteed?

The efficiency would be in principle much higher but depends on the process. The pharmaceutical industry is not efficient itself (many regulatory and control steps and established practices, etc.). So its efficiency regarding unit level is not really high, but again this question is very speculative. It depends on the process more than in the technology.

Pharmaceutical companies

TEVA Pharmaceuticals

Dr. X actually has a leading position in the global commercial sector at TEVA Pharmaceuticals but before that, he was the head of global respiratory marketing also for TEVA.

Teva pharmaceuticals is the world's leading company in generic drugs but it is also investing in personalized medicine in areas such as Multiple sclerosis, Parkinson's disease and Pain reduction.

INTERVIEW

- **Company's position regarding drug personalization**
  - **What's your idea regarding drug personalization? (**Only personalized treatments or also drugs like ibuprofen?**)**

Today, what's happening is that we still live in a much regulated environment (regulative agencies) regarding quality of medicines.

There are also 3D printed drugs that have been launched to the market: Aprecia Pharmaceuticals SPRITAM. And few academic groups are trying adapt characteristics of medicines by using 3D printing. But this is just one aspect. This is manufacturing something that would currently meet the actual quality requirements.

In Glasgow a professor produced in 2012 the Chemputer, but not much has happened since then. The concept in itself is a great concept, it could happen but it will require time. The second part is that there are more and more production of sensors that check heart rate overnight for example but also, other physiological rates to be measured: frequency, color, etc. So, if all this data provided by different sensors would be gathered and combined using big data, it will enable the understanding of diseases and that could make health and diseases more predictive and thus, turn medicine into becoming more preventive instead of just palliative. One example is from analyzing the breathing and heart rate of a new born, you

can predict if he will suffer an infection in the following hours. When the physician sees this patterns, he or she could decide whether they administer directly antibiotics as a preventive measure or they wait prepared until the infection arrives. There are also applications that record and track changes without directly requiring an active role of the patient, for example IPhone can detect changes in how bipolar patients touch the screen and that's an indicator that they are going to suffer an episode.

The combination of this data with the prediction that comes out from that, you can start 3D printing different medicines with the required dosages to each patient. They could even produce it themselves at home if they follow the patterns that the device is showing them.

The second thing is that suppose that Chemputer happens, the API will not be required anymore, that would cause a big change in all the expert system and each individual will get a completely personalized treatment. This is current science fiction. But something as disruptive as this happens, the consequences would be that the pharmaceutical manufacturing would completely change. Nevertheless, this alternative would be more localized, it is not likely that the whole manufacturing process would completely change. The alternative with sensors that help personalized and preventive treatment is more likely (simpler and more feasibility) than the chemputer that will not happen in the next 20 years.

- **How will you produce them?** Smaller batches?

Small batches will be very expensive from a manufacturing perspective, so, 3D printing has a huge advantage. My guess is it will be the winning technology.

Keep in mind though most pharmaceutical therapies, from a clinical perspective, will not need to be personalized, there's limited benefit and significantly increased cost vs. mass manufacturing.

- **How can profits be maintained?**

The profits will be divided between mass produced drugs (generics and common medicine like ibuprofen) plus another business branch that is personalized medicine. The profits will be increased due to the fact that the second market hasn't been completely spoiled and this new production method is one likely possibility to do so.

- **Would the prices of the drugs be higher?**

The costs for that specific tablet would be higher because you cannot compete with the current machines that produce 100.000 tablets. But there could be situations that without this mass production can deliver value and those would cost more but will have a market because the target is different.

- **3D printing of drugs**
  - **What do you think about it? Will it be a reality?**

  I believe that would be more personalization in the future and a technology that can enable that is 3D printers. The other possibility is that there are some diseases that could be obtained in a more convenient way. For example, checking some metrics and applies the therapy based on that. And new technologies in this field will enable new medicines that are not possible today.

- **What's your strategy regarding that**?

TEVA is investing in personalized medicine and generics. Teva explores many different approaches. 3D printing is one of them. I'm however not free to speak about Teva strategies which have not been disclosed publicly, being a NYSE listed company.

- **Production volume**?

3D printing will happen in a small scale personalized and in industrial level from those that can benefit from them.

- **What do you think will happen in the market**? (The first in the market will take all profits? Each company entering the market of drug 3D printing production will take a share?

When 3D printing becomes applied in the market, so added value medicines (like personalized treatments) are offered, two things can happen: a completely new business will emerge with companies specialized in this or big pharmaceutical companies will either discover themselves or buyout those small companies.

- **Anyone is ready yet to enter**?

Where are we? We are not there yet. Mainly due to regulatory and safety concerns and uncertainty of what we would need to do. Also, this would be more likely for products with a small therapy window so you would be able to adapt to patients' needs.

For example, WARFARIN is a medicine that with metabolite measurement, by input in the system it could establish the quantity that your body requires so the patient is treated correctly (is so sensible the system that nowadays many people get overdosed).

- **What would it be the role of the pharmaceutical companies like TEVA?**

The additional value that with the current 3D printing systems is delivered is practically nothing. That's why this methodology has not been applied yet. The chemputer with sufficient investment, it will happen over time. The concept sounds simple and doable but if you want a competent one that can produce any API that is going to be a big challenge.

- **How could Supply chain (logistics) change**?

What would happen in the Supply chain is that the medicines mass produced will not change because whatever you try outside of that system will cost more and will not ensure quality and reliability as it is already offering. So major part of the SC will remain the same but in some specific areas the change would be tremendously. This is a big market where pharmaceutical companies can make money and there is a market opportunity. This would be a new industry that will emerge in the next 5-10 years.

Regulatory experts

For this interview I approached **Mr. Jaap Koster** Director of the Pharmaceutical consultancy service, **Drs. Hans J.L. Meerburg**, a Pharmacists who now works for the Pharmaceutical industry, specifically for Grondmeer Farma B.V and **Drs R.H.L.M. (René) Maassen** who now owns the called Maassen Pharma

Consultancy but who previously worked as a Pharmaceutical Inspector for the Dutch Health Ministry. I was able to approach them in a training event about GMPs that was organized by PC services held in Utrecht, the Netherlands on 4th April 2016. The information written down was gathered through the discussion that the three experts maintained about this topic.

1. Do you think drug 3D printing is a short-term reality or long-term? Or not a reality at all?

3D printing of drugs offers many possibilities: complex medicines (only one pill that contains many drugs), changes in the amount of API dispensed, less spoil product and lower the quantity of excipients.

The main challenge that surrounds this technology is **validation** which includes cleaning and cross-contamination as the main technical concerns. Will many drugs be produced in the same machine? And if so, how would it possible no to mix APIs? To avoid this problem, would it happen that pharmacies will have different **multi-purpose machines**? In the case that one patient was getting the medicine from one machine there wouldn't be those concerns, the problem arises when the same machine provides for many patients. This challenge will require R&D (more knowledge) and an analytical method to analyze this. One way of solving the cleaning problem would be that the parts of the machine that get touched by the ingredients are for a single use.

The following questions will refer to a possible paradigm in which drugs could be 3D printed directly in pharmacies or in hospitals.

2. How would the current GMP practices change to "accept" drug 3D printing? *It comes to ask how the current regulations would adapt to produce drugs in hospitals and pharmacies instead of producing them in a controlled environment like a manufacturing facility.*

Different rules apply in pharmaceutical production and industrial (mass-production). In pharmacies they are not obliged to have a license to produce the products as long as they are tailor-made and thus, small quantities.

3. How a change in GMP affect pharmaceutical companies?

If 3D printing would be applied to the production of tablets there won't be any changes in regulations regarding the end product. The regulations will check whether the product meets the quality requirements and that's it. The benefit of producing this way is that the costs would be reduced, less workers required, less number of machines (less production steps).

4. Will the regulations differ between countries?

In the case of the US and Europe, regulations for oral dosages do not exist so, any change in regulation would be needed. But in other countries like India or China, there are environmental regulations that should be considered that constrict the production area for example clean rooms are required with a D level. Also, many European and American pharmacies do produce or package under similar conditions through it is not required by law.

It is worth to mention too that large scale production of drugs like ibuprofen could not be substituted unless the new production method offers uniqueness, for example, physical characteristics by which

patients can swallow the drugs easily (like what Aprecia Pharmaceuticals has produced). If the product is tailor-made it can be produced in a pharmacy but if not, then mass production is left for pharma. Another possible alternative is that a pharmacy acts like a production center, the other pharmacies get the patients' prescriptions and send them to the other pharmacy who actually prints them. Legally, this alternative is not possible because of trading between pharmacies.

5. What would be required to ensure quality and reproducibility of drug production?

Process validation to ensure reproducibility and quality is required. To ensure that, the disturbances that the process could have need to be assessed until what point they suppose risks.

An important point here as well is *will each tablet be considered as a batch?* If a batch is considered to be each tablet, then **traceability** is easy, it has to be an information record where it is established to whom that tablet was distributed.

6. What are the necessary standards?

Some experts of drug 3D printing have pointed the need of establishing standards regarding materials used and printers.

The standards refer to what is necessary to ensure process validation.

7. How counterfeit drugs could be avoided?

In the case of drug 3D printing **counterfeiting has no sense** in a way that only the manufacturer has the recipe and the ingredients to actually produce the given tablet. If a counterfeit does appear under this alternative of tailor-made production, you directly know who did the fault as all the **distribution path is known**. However, in the possibility of mass production there is a risk of counterfeiting because the process is less controlled (information flow mainly is not controlled). Also, if everyone was allowed to produce their own medicine (by having the printer at home), which is a likely possibility like it is happening for food and medical devices, it is hard to guess how the government would handle this counterfeiting problem.

8. How labelling and packaging would change?

Those will not change unless you produce in large quantities in which different blasters are needed. The information required in the label would be: name of the patient, reference number, dosage, API compound, concentration and location of the production. Also an interesting point is that the **due date will be years** as some studies have proven**.**

Marketing would be the same for custom-made products that already exist. If the products are new, the marketing would be too.

9. Any changes in quality testing?

Pharmacies follow GMP guidelines and also certified labs will play a role here.

Regarding equipment, it will need to get tested to avoid any disturbance but the end product has to follow the same quality requirements that the other tablets. If the product changes, for example, combination of medicines or different properties, then the quality will change too. It will depend on the medicine produced whether the regulations and the quality checks will change or not.

10. Will the FDA regulate the 3D printer or the end product?

FDA or EMEA will ask for process qualification, verification and validation but the regulation applies to the end product, so the tablet produced. But, as previously established, the regulations do not apply in the product obtained in the pharmacy.

Conclusions: Pharmaceutical companies just care about making money, regulatory entities care about quality. Quality goes first, if not, anyone will buy your product.

11. How this production method can reach the market?

First, there are going to be try-outs in hospitals with special diseases. Then, the challenges will be overcome one by one and regulation will be established at the same time.

Main concerns: time of production and volumes.

Products: implants and niche markets that require targeted medication.

Interview analysis

First part of the analysis according to the interview analysis explained in section 2.4.2, is finding key words repeated through the interview transcripts. The second is to classify those key words into groups adding more details:

Table 12. 3D PRINTING EXPERTS. Source: this project

CATEGORIES	KEY WORDS	APPERANCE (%)
Production related	**Expiration date**	**60**
	Stability	20
	Type of medicines	**60**
	Production system	**80**
	Costs	40
	Printer location	**60**
	Production volume	**60**
	Process control	20
	Validation	20
	Complementary technologies	20
	Dosing accuracy	40
Other	Technical requirements	20
	Business model	**80**
Regulatory concerns	Counterfeiting	20
	Standards	20
	Liability	20

	Copyright	40
	Regulatory approval	**60**

CONCLUSIONS:

- HOT TOPICS 60-80% (3 or 4 respondents mentioned them as key points to answer regarding drug 3D printing) are: expiration date, type of medicines, production system, printer location, production volume, business model, copyright and regulatory approval.
- The others are not conclusive → 5 interviews, 1 only key points, some experts didn't know the answer or cannot say.

Table 13 SUPPLY CHAIN MANAGERS. Source: This project

CATEGORIES	KEY WORDS	APPERANCE (%)
Production related	Production costs	50
	Production system	100
	Type of products	100
	Printer location	100
	Production volume	100
	Technological challenges	100
Supply chain related	**Supply chain length**	100
	Supply chain risks	50
	Inventory levels	50
	Supply chain costs	100
	Quality	50
	Reliability	50
KPIs	**Responsiveness**	100
	Agility / Flexibility	100
	Visibility	50
	Efficiency	100
	Costs	100
Business related	**Business model**	100
	Market entrance	50
Regulatory concerns	Counterfeiting	50
	Liability	50
	GMP, standards	50
	Traceability	50
Challenges	Complementary technologies	50

CONCLUSION

- Only 100 means both experts consider important
- 50% doesn't mean is not important.

Table 14. PHARMACEUTICAL COMPANY. Source: This project

CATEGORIES	KEY WORDS
Production related	Type of medicines
	Costs of medicine
	Production volume
Supply chain	Supply chain
Uncertainties/concerns	Regulation uncertainty
	Uncertainty of action
	Safety concerns
Business related	Market opportunity
	Additional value
	Profits
	Business model
	Company's strategy
	Market dynamics

Table 15. REGULATORY AGENTS. Source: This project

CATEGORIES	KEY WORDS
Production	Production system
	Costs
	Type of medicines
Regulation	GMP rules
	Quality
	Safety
	Standards
	Process qualification
	Product qualification
Technical concerns	Cleaning
	Cross-contamination
Challenges	Validation
Non concerns	Traceability
	Counterfeiting

The third step is to generalize the different categories between experts into one. In table 12 the key words are generalized in a table and classified by categories. Also, the actors' opinion of each are specified. The order of each key word is by relevance according to each actor's answers. Some of them are listed as high importance although not all the actors mentioned it; this is because the topic is of strong importance although not of everyone's area of expertise. Also, when the opinions are in bold means that all the actors agreed on that and the key words in bold refer to the most commented between actors.

Table 16. Key words organized by categories. Source: this project.

CATEGORIES	KEY WORDS	ACTOR	OPINION
Production related	**Production system**	Regulators Supply chain 3D printing	**Essential**
	Expiration date	Regulators 3D printing	NO AGREEMENT Equal to determine as current medicines Extreme importance
	Type of medicines	Regulators Supply chain 3D printing Pharmaceutical C.	**Personalized** **Niche markets**
	Printer location	Supply chain 3D printing Pharmaceutical C.	**Pharmacies and hospitals.** At home in the long term.
	Production volume	Supply chain 3D printing Pharmaceutical C.	NO AGREEMENT -Depend on scale and location of the printer - Small customized first (Various actors) - Depend on the need
	Production Costs	Regulators Supply chain 3D printing Pharmaceutical C.	**More expensive** **-**Big market potential - Different market, can't compete current technology. - Not clear overall cost.
	Dosing accuracy	3D printing	**No problem** Current technologies are enough
	Validation	3D printing Regulation	**Key point of the process**
	Stability	3D printing	**Key to determine Expiration date**
	Process control	3D printing Supply Chain	**No problem** As current systems
Technical concerns	Cleaning	Regulators	**Key point**
	Cross-contamination	Regulators	**Key point**
Challenges	Validation -Process and product qualification	Regulators	**Key point**
	Technical requirements	Supply chain 3D printing	NO AGREEMENT Faster printers (some researchers don't agree) Packing systems Cleaning **New materials** Digital tread
	Regulatory approval	Regulators	**Key point**

Regulatory concerns		Supply chain Pharmaceutical C.	
	Copyright	3D printing	Not applicable
	Counterfeiting	Regulators Supply chain 3D printing	Not relevant. Just in case of mass production.
	Standards	Regulators 3D printing	**Key point.** Part of the validation procedure.
	Liability	Supply chain 3D printing	Who prints the medicine, most likely **pharmacist**
	Traceability	Regulators Supply chain	**Advantage of the technology**
	Uncertainty of action	Pharmaceutical C.	**Key point**
	Safety concerns	Pharmaceutical C.	**Key point**
	GMP rules	Regulators	Shouldn't be a problem, as current systems
	Quality	Regulators Supply chain 3D printing Pharmaceutical C.	**Key point**
	Safety	Regulators	**Key point**
Supply chain related	**Supply chain length**	Supply chain	**Key benefit**
	Supply chain costs	Supply chain	**Key benefit**
	Inventory levels	Supply chain	Beneficial
	Supply chain risks	Supply chain	Beneficial
	Reliability	Supply chain	Beneficial
KPIs	**Responsiveness**	Supply chain	**Key benefit**
	Agility / Flexibility	Supply chain	**Key benefit**
	Costs	Supply chain	**Key benefit**
	Efficiency	Supply chain	**Key benefit**
	Visibility	Supply chain	Beneficial
Business related	**Business model**	Supply chain Pharmaceutical C. 3D printing	**3D printed personalized medicine would become another business segment**
	Market entrance	Pharmaceutical C.	Wait and see strategy R&D on Personalized and 3D printing
	Market opportunity	Pharmaceutical C.	Big market segment different from existing medicines.
	Additional value	Pharmaceutical C.	Covering an existing need
	Profits	Pharmaceutical C.	Maintain high monopolistic profits.
	Company's strategy	Supply chain 3D printing Pharmaceutical C.	-**Maintain current production systems + 3D printing** -Move towards 3D printing in the long-term

Performance indicators

Table 17. Delivery performance indicators divided into supply chain drivers, constraints, drivers and performance indicators mass production compared against drug 3D printing. Source: adaptation from Beamon, B. M., 1998; Min, H., & Zhou, G., 2002 with information from the literature review and interview analysis of this master thesis plus discussion with my first supervisor Ir. M.W. Ludema.

	TYPES	SUBTYPES	MASS PRODUCTION	3D PRINTING
SUPPLY CHAIN PERFORMANCE MEASURES	**Responsiveness**	*Minimize stock out probability*	**Low** (variations in demand not easy to adapt unless big inventories)	**High**
		Adjust to demand variance	**Low**	**High**. Production targets customers' needs.
		Delivery reliability		
	Agility	*Lean times*	**Low**	**High.** Less steps in
		Inventory levels		
	Costs	*Minimize length*		
		Minimize inventory level (main driven)	**High**	**Low**
		Minimize obsolete inventory (main driven)	**High**	**Low**
	Asset management	*Capacity utilization*	**Low** large factories with low productivity.	**Low.** Decoupling point is moved to the right.
	Reliability	*Order fulfilment*	**High**	**High**
	Visibility and traceability	*Supply chain transparency*	**Low**	**High** (production process is short and localized)
	Flexibility	*Adapt to demand*	**Low**	**High**
	Efficiency	*Resource usage*	**Medium**. Waste and many steps	Not clear between experts
		Distribution	**Medium**	**High**
		Business	**Not efficient** (regulation, GMP, R&D)	**Not efficient**

KPIs added: efficiency, visibility and agility.

PART C

Stakeholder Analysis

Table 18. Stakeholders' role with mass production and 3D printing. Source: this project.

STAKEHOLDERS	MASS PRODUCTION	3D PRINTING
PATIENT/ CUSTOMER	-Buy and take the medicine	-Same role
PHARMACEUTICAL COMPANIES	-Produce tablets, pills.	-Produce filaments/inks with varying dosages. **Aim**: maintain their competitive strengths and monopoly position.
LOGISTIC FIRMS (from pharmaceutical companies to distributors/ sellers)	- Set-up clusters of manufacturing points close to the end markets	- Transport 3D printers and filaments or inks
HOSPITALS/PHARMACIES	- Distribute medicines -Low power and resources	-Produce and distribute medicines
SUPPLIERS (of pharmaceutical companies)	-Provide raw materials	-Provide 3D printers and raw materials. (divided in the power interest matrix)
DIAGNOSTIC COMPANIES	Provide diagnostic tests	Same role
REGULATORY AGENCIES (FDA)	Establishing standards and controlling quality	Need to establish new regulations and standards.
GOVERNMENTS	High pressure on prices and costs (reimbursement strategies) Pressure on broaden the coverage.	High pressure on proof of concept right now and costs.
PAYERS	Ensure treatments are cost-effective.	Same role
INSURANCE COMPANIES		New medicines and diagnostic tests to cover or not.