BUSINESS MODEL INNOVATION FOR POTENTIALLY DISRUPTIVE TECHNOLOGIES: THE CASE OF BIG PHARMACEUTICAL FIRMS ACCOMMODATING BIOTECHNOLOGIES

A DISSERTATION

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Summary

Potentially disruptive technologies are challenging to commercialize because they are associated with values new to established firms. Without fitting business model innovation, incumbent firms fail to bring new potentially disruptive technologies to the market. The burgeoning literature on disruptive innovation provides only limited recommendations on specific business model elements that can serve to accommodate potentially disruptive technologies. To close this research gap, this thesis explores how big pharmaceutical firms accommodated biotechnologies in the design of their business model innovation to discover successful business model design elements.

A qualitative research approach consisting in three studies is adopted. First, following a systematic literature review on business model research in the pharmaceutical industry, 45 papers are selected and qualitatively analyzed. Second, qualitative semi-structured interviews are conducted with 16 experts in big pharmaceutical firms. The transcripts are analyzed using the qualitative content analysis method. Finally, a cluster analysis is conducted to identify value proposed and delivered by all digital offers of big pharmaceutical firms.

This thesis is the first to describe two business model designs of big pharmaceutical firms from before and since the accommodation of biotechnologies. This research argues that business model designs recommended for the accommodation of potentially disruptive technologies are collaboration portfolios and digital servitization. First, established firms should devise a portfolio of collaboration formats by diversifying breadth of partners (including competitors), and by covering all activities in their value chain. Second, incumbent firms should innovate in the value they offer and how they deliver it to mainstream and new customer segments though bundling their products with complementary services, especially those that are digitally enabled. Digital services serve for back-coupling customers' needs with the producer.

Besides advancing theory on disruptive innovation, the recommended business model design elements can be directly used by top midsize pharmaceutical firms (e.g., Fresenius or Servier) and firms from other industries to commercialize other potentially disruptive technologies. This research supports policy makers in devising strategies for the promotion of the commercialization of potentially disruptive innovations in their specific contexts.

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List of Abbreviations and Acronyms

Apps	Applications for smartphones
B2B	Business-to-business
B2C	Business-to-consumer
Big Pharma	Big Pharmaceutical
BM	Business Model
CMOs	Contract Manufacturing Organizations
CROs	Contract Research Organizations
DBF	Dedicated Biotechnologies Firm
DNA	Deoxyribonucleic Acid
EUR	Euro
FIPCO	Fully Integrated Pharmaceutical Companies
GBP	British Pound Sterling
GSK	GlaxoSmithKline
HCP	Healthcare Professional
IBCO	Integrated Biopharmaceutical Companies
IP	Intellectual Property
KOLs	Key Opinion Leaders
KPIs	Key Performance Indicators
PSPs	Patient Support Programs
QDAS	Qualitative Data Analysis Software
RNA	Ribonucleic Acid
USA	United States of America
USD	United States Dollar

1. Introduction

1.1. Motivation and problem statement

Many incumbent firms that are well managed fail when a certain type of new technologies is introduced to the market (Baiyere & Salmela, 2013; Christensen, 1997; Christensen et al., 2018; Cozzolino et al., 2018; Dan & Chieh, 2008; Danneels, 2004; Fernandez et al., 2019; Schuh et al., 2018; Walsh & Kirchhoff, 2000). For instance, IBM, a leader in the mainframe computer market, was a minor player in the minicomputer market, which was created by firms such as Digital Equipment Corporation and Hewlett-Packard (Christensen, 1997). Xerox lost leadership to Hewlett-Packard and Canon in the tabletop printer and photocopier market (Baiyere & Salmela, 2013; Christensen, 1997). Kodak and Blockbuster are other companies that lost their market leadership when confronted with disruptive technologies (Christensen et al., 2018; Lucas & Goh, 2009). Kodak went almost bankrupt when digital photography was introduced to the market (Lucas & Goh, 2009). The products based on the new technology made polaroid cameras, Kodak's main product and its whole business, obsolete (Lucas & Goh, 2009).

Nevertheless, there are few incumbent firms who did not fail when new disruptive technologies emerged (Baiyere & Salmela, 2013; Christensen, 1997; Dan & Chieh, 2008; Danneels, 2004; Fernandez et al., 2019; Gilbert, 2005; Prasetio & Dhewanto, 2011; Walsh & Kirchhoff, 2000). For instance, in the mechanical excavator industry, from approximately 30 excavator companies in business in the 1950s, four succeeded to switch to hydraulic technology by 1970s and remained in business (i.e. Insley, Koehring, Little Giant, and Link Belt) (Christensen, 1997).

The accommodation of potentially disruptive technologies is a challenge for incumbent firms, because it requires new business model (BM) designs that deviate from their established ones (Christensen et al., 2018; Danneels, 2004; Gilbert, 2003, 2006; Guo et al., 2019; Moreau, 2013; Walsh & Kirchhoff, 2000). To accommodate is "*to consider and include something in a design or plan (e.g., to accommodate wheelchairs, all he had to do was widen the doorways)" (*Cambridge Business English Dictionary©). A BM represents the way a firm creates value propositions, delivers them to their customers and generates profit in the process (e.g. Abdelkafi et al., 2013; Baden-Fuller & Morgan, 2010; Osterwalder et al., 2010; Teece, 2010).

What makes leading firms so successful is precisely their established BMs that have proven successful to bring many technological innovations to the market (Christensen, 1997; Christensen et al., 2018). One key aspect of disruptive technologies proves to be problematic for incumbent firms, namely: Disruptive technologies bring new value propositions (Baiyere & Salmela, 2013; Christensen, 1997, 2002; Gilbert, 2003; Moreau, 2013; Walsh & Kirchhoff, 2000). When incumbent firms try to commercialize disruptive technologies with their established BMs, they fail (Christensen, 1997; Christensen et al., 2018). As Henry Chesbrough said: "*a mediocre technology pursued within a great business model may be more valuable that a great technology exploited via a mediocre business model*" (2010, p. 354).

In conclusion, disruptive technologies are challenging to commercialize because they are associated with values new to established firms in a given industry (Christensen, 1997). Without new BM designs, incumbent firms fail to bring new potentially disruptive technologies to the market (Gilbert, 2003). Hence, success in conducting technology-driven disruptive innovations is closely related to success in adapting or changing existing BM designs (Christensen, 2002; Christensen & Raynor, 2013).

Most research on disruptive innovation focuses on documenting the process of disruption or on defining firm's strategic responses (Adner & Kapoor, 2016; Adner & Snow, 2010; Birkinshaw et al., 2018; Christensen, 1997; Christensen et al., 2018; Gilbert, 2003, 2006; Guo et al., 2019; Petzold et al., 2019). The relatively young theory on disruptive innovation does not fully explore the accommodation of potentially disruptive technologies in the design of existing BMs of established firms. Existing research is limited mainly to two aspects: (1) defending the imperative to innovate established firms' BMs and (2) new modes for resources acquisition and capacity building. In the pioneering work of Christensen (1997), followed by Gilbert (2003), Guo et al. (2019), Prasetio and Dhewanto (2011) and Walsh and Kirchhoff (2000), the authors argue for new BM designs allowing established firms to discover new customer segments and their new needs without recommending any specific design elements. Regarding the second aspect, researchers identified at least three modes for the acquisition of new resources and the building of new capabilities: licensing, mergers and acquisitions (Birkinshaw et al., 2018; Christensen, 1997; Cozzolino et al., 2018; Danneels, 2004). However, their research did not systematically explore all possible collaboration formats in relation to the accommodation of disruptive technologies in BM designs.

Hence, literature on the accommodation of disruptive technologies remains insufficiently explored (Christensen et al., 2018; Danneels, 2004; Gilbert, 2003), at least regarding the identification of BM design elements for the accommodation of potentially disruptive technologies. This work aims to contribute to reducing this gap with a special focus on BM design elements for the creation and delivery of values related to potentially disruptive technologies. This research's objective, question and sub-questions are presented next.

1.2. Research objectives and research questions

This work aims to reduce the above-identified research gap and contribute to the development of the theory of disruptive innovation by identifying possible BM designs capable of accommodating potentially disruptive technologies. Hence it revolves around the central question of: **How could established firms accommodate potentially disruptive technologies in the design of their BMs**? The specific case of the accommodation of biotechnologies in the design of big pharmaceutical (Big Pharma) firms' BM is selected for this research.

When biotechnologies first emerged, many experts predicted the fall of established Big Pharma firms (Gassmann et al., 2018). However, Big Pharma firms remain atop of their industry and accommodated potentially disruptive biotechnologies by changing their BM (Birkinshaw et al., 2018; Galambos & Sturchio, 1998). Big Pharma firms are companies specializing in medical products with yearly revenues above 10 billion USD (United States Dollar). This research excludes medical products other than prescription drugs for human use (e.g., vitamins or medical devices). Biotechnologies are techniques for manipulating living organisms, such a molecular genetics and recombinant DNA, that use genetically modified bacteria and yeast to produce drugs (Anand et al., 2010). They are potentially disruptive technologies because they have the potential to render other types of drugs obsolete. For instance, certain biotechnology-based drugs (e.g., Zolgensma®) offer customers the unprecedented value of curing incurable diseases. Zolgensma® (by Novartis) is a gene therapy that cures young children suffering from spinal muscular atrophy, an uncurable rare disease. Sold for 2.1 million USD per patient treated, this drug is the most expensive drug ever sold (Staff, 2021).

In conclusion, the specific research question guiding this work is: **How did Big Pharma firms accommodate disruptive technologies in the design of their BM?** It is divided in four sub-questions.

1. What BM designs of Big Pharma firms, from before and after the accommodation of biotechnologies, can be conceptually derived from the scientific literature?
2. What BM designs from before and after the accommodation of biotechnologies are accurate to the reality of the practice?
3. In which collaboration formats did Big Pharma firms engage to create value from biotechnologies?
4. What digital values, related to biotechnology-based prescription drugs. Are delivered by Big Pharma firms?

Having defined specific research sub-questions, the following section details the methodological approach of this work and presents its overall structure.

1.3. Procedure and structure of the work

As previously stated, more empirical observations are required to contribute to the development of the theory of disruptive innovation (Baiyere & Salmela, 2013; Christensen, 2006; Christensen et al., 2018), especially with respect to BM designs for potentially disruptive technologies. Because there is only very limited research related to this specific research focus, an exploratory and qualitative research is needed and will be followed. Qualitative researchers generally have an interpretivist epistemology and constructionist ontological orientation (Bryman & Bell, 2015; Creswell, 2009). This epistemological and ontological view means that this research does not use deductive strategies to test theories but rather an inductive approach to contribute to theory building. As seen above, for each of the three research questions a different qualitative research method is used. The sum of these studies explores how Big Pharma firms accommodated biotechnologies in the design of their BM, by providing the most accurate description possible of their BMs before and after the advent of potentially disruptive biotechnologies.

This work is divided in six chapters (see Figure 1). The next chapter introduces the theoretical background and key concepts underlying this thesis, as well as the context of the pharmaceutical market and a drug's life cycle.

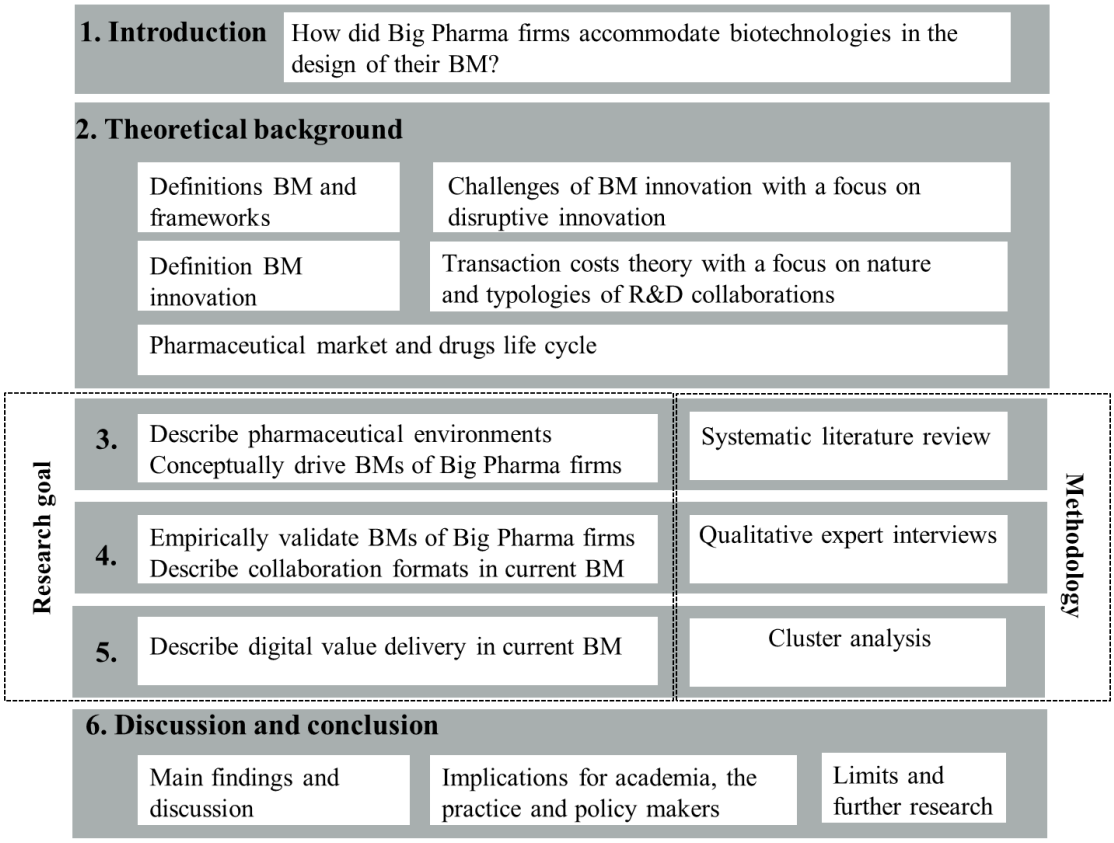
Chapter 3 focus on the first research sub-question through a systematic literature review on BM research in the pharmaceutical industry. In this chapter, the method of is described, and conceptually derived old and new BMs, are presented.

Chapter 4 focus on both the second and third sub-research questions. The method of qualitative expert interviews is followed. Thus, after describing this method, the author presents the results in the form of validated of BM designs and the extend of collaboration formats of Big Pharma firms.

In Chapter 5, the focus is on the last research sub-question. An empirically study is designed by extracting data from secondary sources and grouping them using the method of cluster analysis. This method is presented, and the resulting clusters of digital value proposed and delivered by Big Pharma firms are described.

In the last chapter, the main findings are discussed and implications for practice, policy makers and academia are derived as well as the limitation of this work and suggestions for further research are outlined.

Figure 1. Structure of the thesis (Source: Own figure)



2. Background: Theory and Context

2.1. Business model definitions and frameworks

BM research is an important field for management research. The term BM has been part of the business jargon for a long time (Bellman et al., 1957; Casadesus-Masanell & Ricart, 2010). Its importance increased in the 90s during the internet boom (Demil & Lecocq, 2010; Magretta, 2002) and has become a buzz word both in the scholarly and non-scholarly debates ever since.

BM is a concept that can be distinguished from related terms such as strategy and operation or tactic. Casadesus-Masanell and Ricart (2010, p. 195) argue that a BM "*is a reflection of the firm's realized strategy*". However, an external observer that observes a firm's BM at a defined time, in a specific contingent situation, will not be able to observe the firm's strategy. BM is also distinct from tactic or operation (Casadesus-Masanell & Ricart, 2010; Osterwalder, 2004). A tactic represents the decision from residual options that a firm's BM still leaves open on an operation level (Casadesus-Masanell & Ricart, 2010). Consequently, BM is the layer between strategy (vision and goals) and operations (organization and workflow) (Osterwalder, 2004).

To this day, there is no common consensus among scholars on a unique definition of a BM (e.g. Casadesus-Masanell & Ricart, 2010; Johnson, 2010; Magretta, 2002). For instance, Shafer et al. (2005) conducted a systematic literature review and identified 12 different ways to define a BM such as *"architecture*", "*strategic"*, or *"representation*" of the business. Magretta (2002, p. 87) refers to BMs as "*stories that explain how enterprises work"*. Osterwalder et al. (2010, p. 14) see a BM as *"the rational of how an organization creates, delivers and captures value".* As for Zott and Amit (2010) they take another angle to define the essence of a BM. In their view, a BM is assimilated to an activity system that describes all activities necessary to generate profit for the focal firm and its partners by fulfilling customers' needs. The BM spans the firm's boundaries to include partners' activities that contribute to the overall value created for customers (Zott & Amit, 2010). If a firm creates more value with its BM than its competitors, it holds a potential advantage (Magretta, 2002; Zott & Amit, 2008). Chesbrough (2010) defends a technology driven view of a BM, and refutes the existence of an objective value for a technology *per se*.

He emphasizes the need for an appropriate BM to commercialize a technological invention and to express its latent economic value. Value is *"an economic concept, not primarily measured in physical performance attributes, but rather what a buyer will pay for a product or service*" (Chesbrough & Rosenbloom, 2002, p. 534). Value represents the relation between costs and benefits perceived by a particular stakeholder (Abdelkafi et al., 2013). *"A viable business model must provide value to the customer that is higher than the costs for providing it, and then capture the difference"* (Williander & Stålstad, 2015, p. 18). Profitable customer segments are a necessary condition for the survival of any company (Osterwalder et al., 2010). A customer segment is a grouping of many customers that have similar attributes such as needs, behavior, distribution channels, relationships and willingness to pay (Osterwalder et al., 2010). In a BM, more than one customer segment can be defined and the firm decides which segments to serve and which to ignore (Osterwalder et al., 2010).

In conclusion, many leading scholars in the BM research field agree that a BM describes necessarily at least the following dimensions (e.g. Abdelkafi et al., 2013; Chesbrough, 2010; Chesbrough & Rosenbloom, 2002; Demil & Lecocq, 2010; Gassmann et al., 2014; Magretta, 2002; Osterwalder et al., 2010; Teece, 2010):

- The way or logic to earn money. The value capture dimension refers to the share of the value, created in the marketplace, that the company retains for itself. It can be simplified to the cost structure and revenue streams.

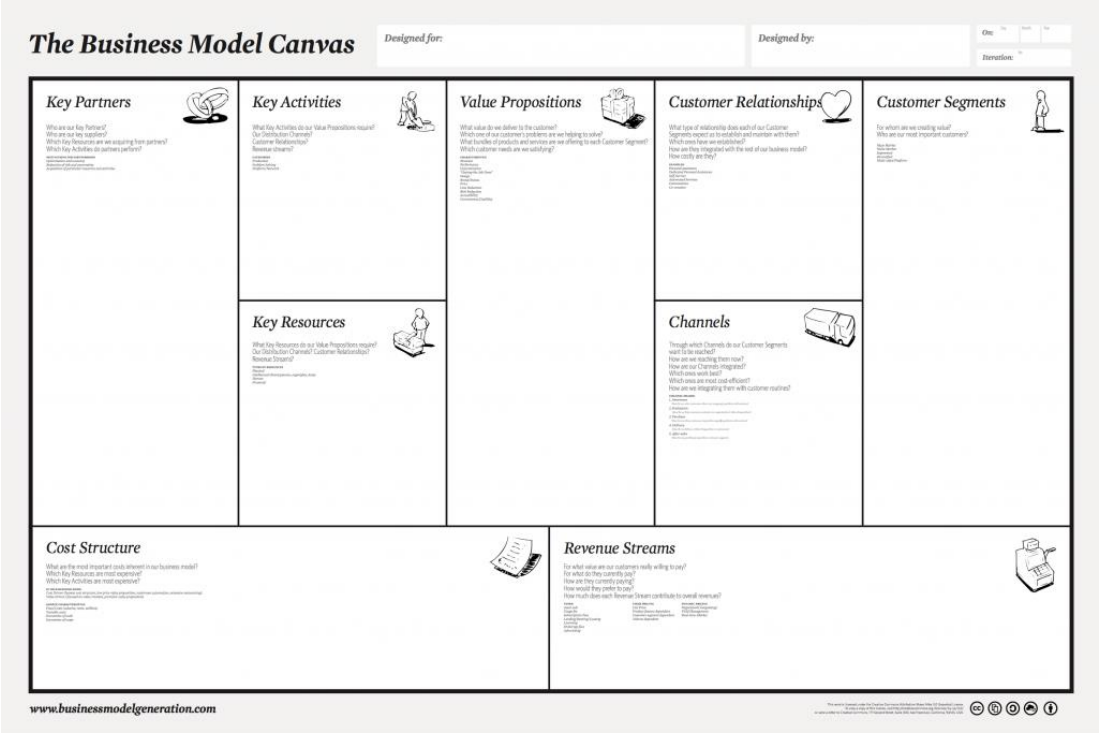
- The way a firm creates value for its customers. The value is created by key activities that transform resources into offers or value positions. The transformation can be supported by partners.

- The value a company offers and how it is delivered to its customers. The value delivery describes the value proposition that a company offers to one or many customer segments based on bundles of products and/or services.

While Casadesus-Masanell and Ricart (2010) argue for a description of a firm's BM free from any constraining frameworks, there are many frameworks developed in the literature, which describe a firm's BM with varying degrees of abstraction and structuring. Three frameworks are predominantly used to capture the design of a firm's BM.

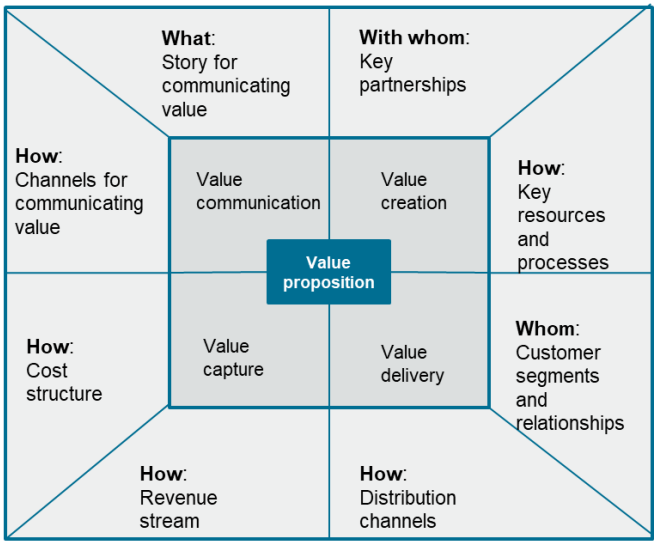
The popular "Business Model Canvas" developed by Osterwalder et al. (2010) describes nine building blocks that reflect four main areas of a business: Customers, offers, infrastructure and financial viability (see Figure 2).

Figure 2. The Business Model Canvas (Source: Osterwalder et al., 2010)



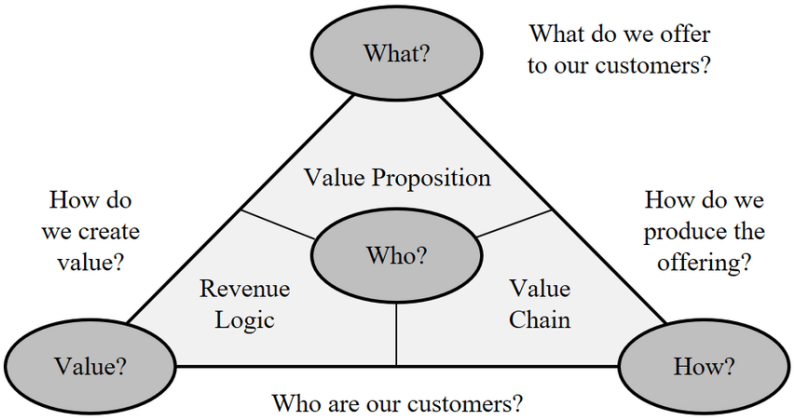
Abdelkafi (2012) have transformed the nine building blocks defined by Osterwalder et al. (2010) into more structured value-oriented dimensions (see Figure 3). In this framework, four value dimensions (value creation, value delivery, value communication and value capture) are placed around the central value proposition, to emphasize the role of each dimension in the total value creation of the whole BM (Abdelkafi, 2012; Abdelkafi et al., 2013).

Figure 3. The Business Model Framework (Source: Abdelkafi et al., 2013)



Gassmann et al. (2014) developed their own visual artefact for designing business models, the so-called "magic triangle" (see Figure 4). The model counts four dimensions. The center of the model is the customer surrounded by value position, value chain, and profit mechanism (Gassmann et al., 2014). For them "*a business model defines who your customers are, what you are selling, how you produce your offering and why your business is profitable"* (Gassmann et al., 2014, p. 7).

Figure 4. The magic triangle of business models (Source: Gassmann et al., 2014)



For this work, an adapted version of the BM framework of Abdelkafi et al. (2013) is used (see Figure 5). This framework is preferred to the two others because it structures BM design elements in clear dimensions and sub-dimensions. The adaptations are made to reflect the above-mentioned definition of a BM. Consequently, value communication is eliminated. Distribution channels are part of company's value chain or key activities.

Value position figures as a sub-dimension of the value delivery dimension. In this new framework, firm-specific BM element are filled in the empty right column.

Figure 5. Business model framework (Source: Own figure adapted from Abdelkafi et al., 2013)

Dimension	**Sub-dimensions**	
Value delivery	Value proposition	
	Customer segments & relationships	
Value creation	Key activities	
	Key partners	
Value capture	Revenue streams	
	Cost structure	

2.2. Definition and challenges of business model innovation

Over time, BMs naturally change, at least, due to firms' changing and evolving environments (Gebauer, 2020). New technologies, changes in regulation and laws, and changing competitive environments are only a few of the reasons that can render a BM not profitable anymore (Linder & Cantrell, 2000). In response to constant pressures, "*firms tweak, twist, and totally revamp their business models in a wide variety of ways"* (Linder & Cantrell, 2000, p. 10). In sum, technological innovation and market distress are two primary conditions that drive BM innovation (Budde Christensen et al., 2012). Firms pursue BM innovation through a process of learning, experimentation and adaptation (Bohnsack et al., 2014).

2.2.1. Definition of BM innovation

The goal of BM innovation lies in identifying new ways to generate value (Bohnsack et al., 2014). For the business world, BM innovation is correlated with competitive advantage, which in several cases results from a trial and error rather than from a systematic process. In fact, new companies typically change the design of their BM at least four times until it is profitable (Johnson et al., 2008). BM innovation is another form of innovation than product or process innovation (Gassmann et al., 2014). The scientific literature contains several definitions of BM innovation. This is not surprising, since there is not yet a consensus on a definition of a BM.

Scholarly perspectives on BM innovation are segmented in two branches. Researchers see BM innovation either as an outcome or as a process (Foss & Saebi, 2017).

Innovation is seen as the process of transformation from one state to the other. In the process or transformational approach, researchers are focusing only on changes in the firm (Demil & Lecocq, 2010). Researchers focus on a single aspect of the firm and study its change, evolution or adaptation using the concept of BM as an analytical tool (Demil & Lecocq, 2010). For instance, Diestre and Rajagopalan (2012) explore the selection of Dedicated Biotechnology Firms (DBF) of Big Pharma partner firms, by studying their value creation and appropriation mechanisms.

In the second branch, when the term BM innovation refers to the outcome of a transformation process, rather than to the process itself, researchers consider a BM as a static object (Demil & Lecocq, 2010). In the outcome or static approach, a BM innovation is a change in the mental model or logic of a company (Foss & Saebi, 2017). Researchers understand a BM as the blueprint of a company. In this approach, the most important word is model. A model is *"always a simplified representation of a particular domain of reality"* (Bossel, 2007, p. 18), but not a one-to-one representation of it (Abdelkafi, 2012). A typical outcome of such research is building typologies that focus on describing BM elements and to research the relationship between a BM design and a firm's performance (Demil & Lecocq, 2010). For instance, Remane et al. (2017) developed a BM pattern database consisting of 182 patterns. They organized their patterns in a morphological box according to their specific impact on firm's BM dimensions such as revenues or value proposition.

In this thesis, the focus is on understanding how Big Pharma firms accommodated biotechnologies in the design of their BM. This research adopts a static approach to BM innovation research. This work describes blueprints of the design of the traditional and new BMs of Big Pharma firms. The static approach is characterized by its depth of analysis and the need for the confirmation of the coherence of BM design elements.

In general, the way BM innovation is defined varies according to the scope of BM changes and their novelty level. Researchers do not agree on the number of necessary changes in an established BM to qualify the new design as a BM innovation. On the one hand, for Markides (2006) and Bucherer et al. (2012), a BM innovation is a *"fundamentally different business model"* (Markides, 2006, p. 20) that *"deliberately changes the core elements of a firm and its business logic"* (Bucherer et al., 2012, p. 184). For instance, Amazon's BM design is considered a BM innovation since it differs dramatically from the BM of Barnes & Noble (Markides, 2006).

On the other hand, Abdelkafi et al. (2013) consider any change in at least one of the BM value dimensions as a BM innovation. Gassmann et al. (2014) argue that a change in a unique BM dimension can be described either as a product, process, or organizational innovation. They have a position is in the middle of the spectrum of opinions, including a higher novelty level than Abdelkafi et al. (2013) and non-breakthrough BM innovations (Gassmann et al., 2014). They define a BM design as an innovation, when at least two out of four dimensions of the magic BM triangle are changed (Gassmann et al., 2014). For instance, Dell's direct selling BM is defined as a BM innovation since both the value delivery and value creation are new. Dell developed a digital platform allowing customers to customize their computers and directly order them, with lower prices than competitors (Gassmann et al., 2014). The definition of a BM innovation provided by Gassmann et al. (2014) is preferred, for the reasons above-mentioned.

2.2.2. Challenges of BM innovation

At least three core challenges are found in the literature to describe the difficulties faced by companies to develop BM innovations (Gassmann et al., 2014, p. 11):

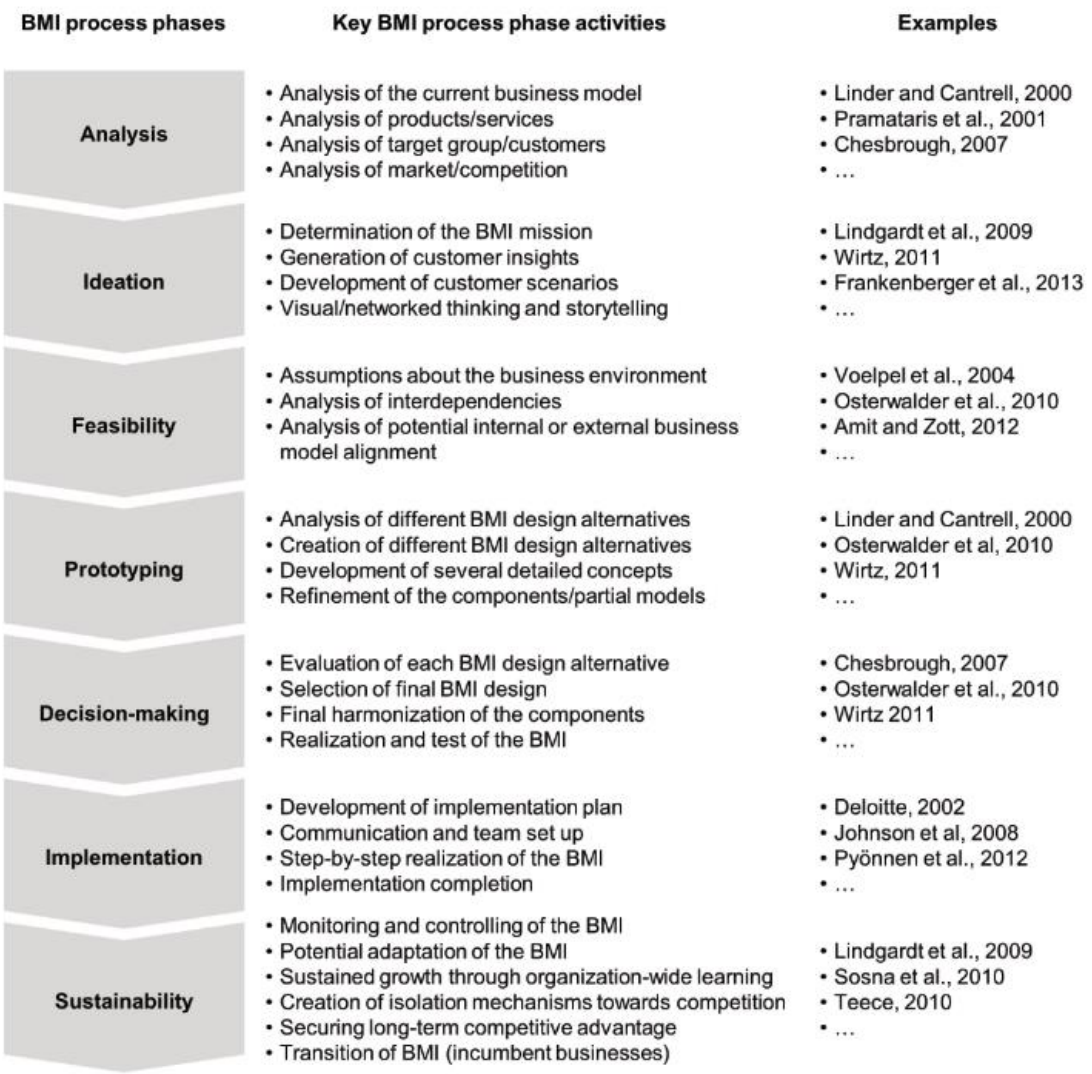
- *"Thinking outside of one's own dominant industry logic is not a simple matter. Mental blocks hamper the development of fresh ideas.*
- *The difficulty of thinking in terms of business models rather than of technologies and products: People prefer physical technologies and products they can see and understand. Most find it much more challenging to think in terms of the more abstract world or business models.*
- *The lack of systemic tools… innovation is a discipline that needs to be managed like any other. Admittedly, it needs methods and processes. Managers also need functional tools for business model innovation".*

The second challenge of thinking in BMs rather than in products or processes is reinforced by many myths (Gassmann et al., 2014). For instance, some managers believe that a BM innovation only stems from exceptional technologies, or require ideas new to the world, or can only be led by creative and lucky geniuses (Gassmann et al., 2014).

Regarding the third type of challenges, different methods and tools have already been defined in the scientific literature to conduct and manage BM innovation.

For instance, there is a three-step process developed by Linder and Cantrell (2000) consisting of the (1) identification of the current BM, (2) developing a new and (3) selecting a change mode. Frankenberger et al. (2013) argue for a four-step process for BM innovation (4I-framework) that consists of: initiation, ideation, integration, and implementation. Meanwhile, the BM design process of Osterwalder et al. (2010) has five phases: Mobilize, understand, design, implement, and manage. Finally, the most comprehensive method found to manage BM innovation is developed by Wirtz and Daiser (2018) and is based on systematic literature review of several BM innovation processes (see Figure 6).

Figure 6. Generic business model innovation process with key activities (Source: Wirtz & Daiser, 2018)



Finally, the first mentioned challenge was the difficulty of thinking outside of the industry's dominant logic (Gassmann et al., 2014).

Bohnsack et al. (2014) find that an industry's dominant logic is not the only path-dependent behavior that constricts firms' openness to innovation. The path-dependent behavior constrains new ideas that would bring companies on a completely new and unexplored path (Bohnsack et al., 2014). Three concepts constitute the path-dependent behavior of companies: (1) the dominant logic, (2) complementary assets and (3) contingent events (Bohnsack et al., 2014), which are explained in the following.

Dominant logic derives from a firm's existing BM. The resulting cognitive constraints lead managers to force new technologies to be commercialized by the dominant BM regardless of their fit (Bohnsack et al., 2014; Chesbrough & Rosenbloom, 2002).

According to Chesbrough and Rosenbloom (2002, p. 531) "*a firm's current businesses influenced its choice of likely future businesses"*. **Complementary assets** are a requirement to the successful commercialization of an innovation (Teece et al., 1997). Bohnsack et al. (2014) found that established companies create complementary assets from existing and new products and services. Firms usually maintain a certain level of coherence between neighboring activities because experience in '*related*' technologies helps entering new business areas by reducing the related costs (Teece et al., 1997).

"*A regime of appropriability refers to the environmental factors, excluding firm and market structure, that govern an innovator's ability to capture the profits generated by an innovation*" (Teece, 1986, p. 287). A contingent event is to some high extend a similar concept to the appropriability regime. **Contingent events** refer to a changing context which could potentially be disruptive to an organization (Bohnsack et al., 2014). In fact, incumbent firms buffer pressures raising from contingent events through their important financial resources and by holding to their dominant logic (Bohnsack et al., 2014). On the other hand, entrepreneurial firms need to continuously adapt their BMs to contingent events.

Teece (1986) explains a firm's profitability levels from an innovation through the same concepts used to define a firm's path-dependent behavior: (1) dominant design paradigm, (2) complementary assets, and (3) appropriability regimes. The three concepts determine a company's share of value captured from one innovation (Teece, 1986) and can simultaneously explain its challenges with other BM innovations (Bohnsack et al., 2014).

Consequently, a whole theory has been dedicated to explaining the failures of incumbent firms consequently to their strong path-dependent behavior. Through the last two decades, Clayton Christensen argued that well-managed and innovative firms atop of their industries failed when they were faced with disruptive innovation (Christensen, 1997, 2006; Christensen et al., 2018). A certain type of technology is disruptive because it requires resources, processes and values that are new to the industry (Christensen, 1997). Incumbent firms fail at commercializing disruptive technologies because their resource attribution processes and values are highly dependent on needs of current customers and investors (Christensen, 1997). What Christensen calls resources, processes, and values of a firm can be referred to as its dominant BM.

In other terms, these firms fail because they force new technologies to be commercialized by their dominant BM, regardless of whether they fit. In conclusion, incumbent firms fail in the face of a certain type of BM innovation because of constraints related to their path-dependent behavior. In the following, disruptive innovation is defined and strategies to respond to it are described.

2.3. Disruptive innovation

2.3.1. Definition of disruptive innovation

Christensen (1997) observes the decline of many well managed incumbent firms at the hand of new entrants that disrupt the market from the bottom with less sophisticated technologies. First, he introduces a distinction between sustaining and disruptive technologies (Christensen, 1997). Sustaining technologies, either radical (discontinuous) or incremental are fostering an improved performance of existing products, according to performance measures that are historically valued by mainstream customers (Christensen, 1997). On the other hand, disruptive technologies bring a value proposition that is new to the industry and are *"typically cheaper, simpler, smaller, and frequently, more convenient to use"* (Christensen, 1997, xv). These attributes of disruptive technologies are likely to be specific to industries observed by Christensen and do not represent a definition of disruptive technologies (Walsh & Kirchhoff, 2000).

The scholarly discourse on disruption grew and distinguishes between disruptive technologies and disruptive innovation (Christensen et al., 2004; Christensen, 2006; Christensen et al., 2018; Christensen & Raynor, 2013; Dan & Chieh, 2008; Prasetio & Dhewanto, 2011; Tadao Kawamoto & Giovinazzo Spers, 2019). When discussing the theory of disruption, the term disruptive technology is replaced with disruptive innovation since the theory can be applied to innovation driven by new services and BMs as well as new technologies (Christensen et al., 2004; Christensen et al., 2018; Christensen & Raynor, 2013). Disruptive innovations are innovations that *"either create new markets, bring new attractiveness to non-consumers, or offer more convenience, at lower prices, to lower-income consumers in an existing market"* (Christensen et al., 2004, p. 321). In sum, disruption is a relative phenomenon that is not equivalent to destructive innovation. Certain authors distinguish between new-market and low-end disruptive innovations (Christensen & Raynor, 2013; Govindarajan & Kopalle, 2006; Prasetio & Dhewanto, 2011; Tadao Kawamoto & Giovinazzo Spers, 2019).

Innovations that are driven by disruptive technologies are defined as disruptive innovations (Christensen, 1997; Christensen et al., 2018; Dan & Chieh, 2008; Tadao Kawamoto & Giovinazzo Spers, 2019; Walsh & Kirchhoff, 2000). This thesis focuses only on technologies driven disruptive innovation. The case of the insulin pens commercialized by Novo Nordisk as of 1985 is an exemplary case of a disruptive innovation driven by new technologies. Eli Lilly is one of the largest pharmaceutical firms, which created and led the insulin market in 1923. Soon, competitors such as Nordisk Insulin Laboratorium (later Novo Nordisk), started producing and selling their own animal insulin in Europe. In the following years, Eli Lilly and its competitors innovated in the technologies in their products based on two performances measures valued by physicians: Purity and time-profile of insulins (Christensen, 1996). In 1970, Eli Lilly partnered with Genentech (DBF), to genetically engineer bacteria able to produce the first human insulin (Humulin®) (Christensen, 1996). Eli Lilly spent nearly 1 Billion USD to introduce Humulin® in a large scale (Christensen, 1996, 1997). This 100% pure insulin did not get the market response Eli Lilly expected. A competitor introduced a new technology to administer the sufficiently purified animal insulin and disrupted Eli Lilly diabetes market position. As it happened, developing countries (mainstream customers) were quite satisfied with the quality of the purified animal insulin that has been reached in 1970s (Christensen, 1996).

The purity of the insulin administered was not the more pressing problem, but how it was administered to patients. As insulin need to be self-injected many times a day, patients delayed their treatments until they had the necessary conditions for the injection, often waiting to be home (new syringe, cooled medicine, and discreet place). The irregularity of the patients administration of their prescribed treatments lead to avoidable complications and reduced life expectancy (Christensen, 1996). Therefore, the introduction of the insulin pen was a disruptive technological innovation. Unlike syringes, pens are preloaded with insulin that is stable at room temperature and are simple and convenient to use: simply twist the pen to get new needle, dial a dose, and inject the insulin. Eli Lilly's direct competitor, Novo Nordisk, was the one to introduce the first insulin pen, the NovoPen® in 1985.

In conclusion, the technological and breakthrough innovation of human insulin is defined as sustaining innovation since it happened along the performance measure valued by mainstream customers (purity).

The Novo pen is a disruptive innovation. The performance measure on which it is founded are new to the industry: convenience of administration of the treatment. The insulin pen is not only a product innovation, but a BM innovation since more than one dimension of Novo Nordisk's BM changed. NovoPen® affects how value is created (value chain) as well as its revenue mechanisms. In fact, the selling of the insulin pen followed a so-called razor and blade revenue model, in which case, the pen was sold at a low price and revenues were made form locking patients with the specific insulin cartridges of Novo Nordisk. In conclusion, succeeding with adopting disruptive technologies in the design of a firm's existing BM requires a BM innovation (Christensen, 1997).

2.3.2. Research fields on disruptive innovation

Many authors focused on documenting firms' strategies to respond to the threat of disruptive innovation (Birkinshaw et al., 2018; Christensen, 1997; Christensen et al., 2018). Creating an autonomous organizational subunit within the established firm is among the most effective strategies to respond to disruptive innovation (Christensen, 1997; Christensen & Raynor, 2013; Gilbert, 2006). If companies decide to carry the BM innovation internally, they need to make sure that the emerging market becomes "*big enough, fast enough, to make a meaningful dent on the trajectory of profit and revenue growth of a large company*" (Christensen, 1997, p. 133).

Several other strategic responses to disruptive innovation have been mentioned in the literature, such as acquisitions of new firms (Birkinshaw et al., 2018; Christensen, 1997), spin-offs of independent organizations (Christensen, 1997), and boost the old technologies to delay the disruptive innovation (Adner & Kapoor, 2016; Adner & Snow, 2010). By establishing a spinoff organization, incumbent firms "*[p]lace responsibility to commercialize disruptive technologies in organizations small enough that their performance will be meaningfully affected by the revenues, profits, and small orders flowing from the disruptive business in its earliest years"* (Christensen, 1997, p. 133). Acquisition makes the most sense if the acquired organization has completely different BM (processes and values) that match the requirements of the disruptive technology (Christensen, 1997). Regardless of their strategic response, successful firms perceive potentially disruptive technologies not as a threat but rather as an opportunity for growth (Fernandez et al., 2019; Gilbert, 2005, 2006; Prasetio & Dhewanto, 2011).

Another research field aims at specifying the process of disruption (Christensen, 1997, 2002, 2006; Christensen et al., 2018; Gilbert, 2003; Petzold et al., 2019). For instance, Gilbert (2003) defines three phases of disruptive innovation:

1. Finding new customers and creating new markets,
2. Designing new BMs that would allow firms to serve the new market profitably,
3. Remaining with the new customers and BMs, since disruptive innovations reduces the growth potential of the old markets and profitability of old BMs.

A third research field concerns the accommodation of disruptive technologies. Through their empirical studies or examples from the practice, researchers in this field urge managers to devise adapted BM designs for potentially disruptive technologies. Disruptive innovation creates new emerging markets that require a different calculation of profitability, often at smaller scale (Christensen, 1997; Walsh & Kirchhoff, 2000). The best way to ensure the appropriate BM for the adoption of a disruptive technology is to *"match the size of the organization to the size of the market*" (Christensen, 1997, p. 127). When disruptive innovations initially emerge in a market, their full value is still to be discovered by manufacturers and customers (Christensen, 1997). It is imperative to discover needs of new customers (Christensen, 1997; Gilbert, 2003; Prasetio & Dhewanto, 2011).

For instance, Novo Terapeutisk Laboratorium (currently Novo Nordisk) discovered that diabetes patients were more in need for a better way to administer their insulin rather than a purer form of insulin (Christensen, 1997). The products or services introduced by the firms need to target new niche markets (Christensen, 1997; Guo et al., 2019; Walsh & Kirchhoff, 2000). When Eli Lilly licensed from the University of Toronto the miraculous insulin and provided it for 25.000 American patients in 1923, it created an emerging niche market for biologic drugs. Firm should consider different collaboration formats as new modes of resource acquisition (Birkinshaw et al., 2018; Christensen, 1997; Cozzolino et al., 2018; Danneels, 2004). Researchers show that technologies licensing, mergers and acquisitions are among the collaboration formats that are successful to build new capabilities (Birkinshaw et al., 2018; Christensen, 1997). The development of the first biotechnology-based drug (Humulin®) was a result of the collaboration of Eli Lilly with a small biotechnologies firm (Genentech). Disruptive innovation require firms to engage with new key partners and create new value networks (Moreau, 2013). In the following, a theoretical input on the nature and typologies of collaboration formats is provided.

2.4. Collaborations and value creation

Nowadays, competition and globalization are forces that prevent any global firm from relying solely on its internal resources and capabilities to remain competitive (Contractor et al., 2010; Martínez-Noya & Narula, 2018). The need to collaborate with external partners is more evident in knowledge and technology intensive sectors such as the pharmaceutical industry (Martínez-Noya & Narula, 2018). Firms engage in collaborations for many different reasons, such as *"accessing complementary resources to develop new or improved products or processes, explore new markets, achieve lower costs, mitigate risks, or reduce time-to-market*" (Martínez-Noya & Narula, 2018, p. 197).

Collaborations can be classified, according to partners' types, into institutional, vertical or horizontal (Martínez-Noya & Narula, 2018). Vertical partners are adjacent firms, which are part of the value chain, operate in related industries, such as clients or supplier (Martínez-Noya & Narula, 2018). Horizontal partners are firms engaged in similar value activities to various extends, such as competitors (Martínez-Noya & Narula, 2018). For firms, universities or research centers are typical example of institutional partners (Martínez-Noya & Narula, 2018).

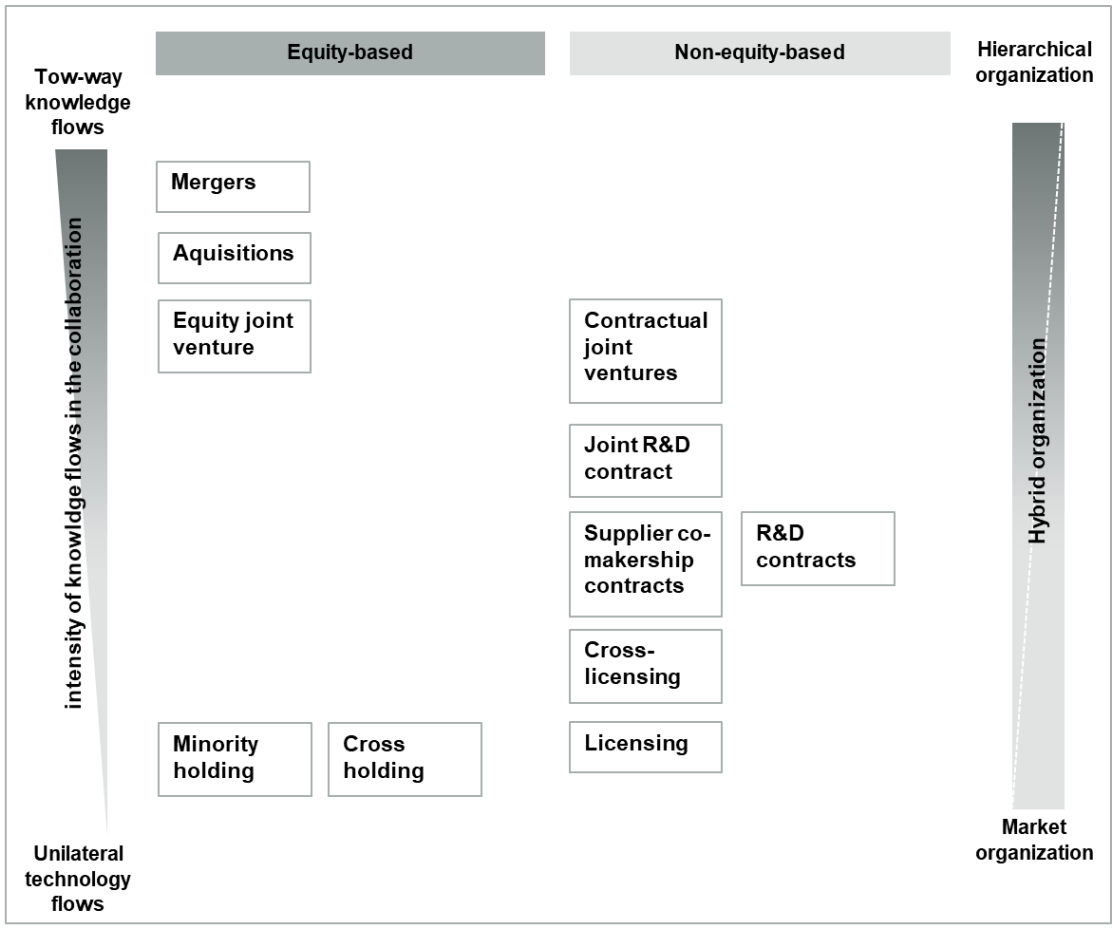
Furthermore, collaborations can also be categorized into equity-based and non-equity-based agreements (Hagedoorn, 2002) according to the market-hierarchy continuum of inter-firm alliances described in the traction costs theory (Williamson, 1975). In the following, relevant aspects of the transaction costs theory and common collaboration formats are presented in brief.

2.4.1. Transaction costs theory

Transaction costs were first introduced in the economic discussion by Coase (1937), but remained largely ignored until the early 1970s (Picot & Dietl, 1990). It was mainly the lifelong work of Nobel prize winner Oliver Williamson that gave the theory its current basis (e.g. Williamson, 1975, 1991, 2005). The transaction cost theory focuses on the organization of economic relationships (Williamson, 2005). Different organization boundaries such as companies, cooperation, markets and authorities are considered alternative forms of organizing and distributing economic activities (Williamson, 2005). The starting point of the reflections of Williamson (1975) is the question of why one part of economic relationships is via the market, while the other part is hierarchical.

The aim of the transaction cost theory is to identify the organization-relevant properties of transactions and to determine the most efficient form of coordination for each type of transaction (Williamson, 2005). It deals with market, hierarchy, and hybrid governance forms of transactions (Williamson, 1991). Hierarchical economic relationships are coordinated with partial elimination of the price mechanism (Picot & Dietl, 1990). Market transactions include, above all, information, communication and coordination costs, such as search costs, initiation costs, agreement costs, processing, adjustment and control costs (Coase, 1960). Hybrid governance forms share characteristics of market transactions while benefiting from enhanced monitoring and low bureaucratic costs, which are associated with hierarchical organization forms (Oxley, 1997). Based on the transcription costs theory, collaboration can take many structural and organizational forms. The most common ones are in Figure 7.

Figure 7. Overview of common collaboration formats (Source: own figure based on Narula & Martínez-Noya, 2015; v. Werder, 1989)



2.4.2. Types of collaborations

Minority and cross holding are situations in which companies own less than half of the shares in another company. More specifically, when a publicly traded corporation owns stock in another publicly traded company, it is called cross holding.

Licensing and cross-licensing contracts relate to exploitation of intellectual property (IP) rights (Drozdoff & Fairbairn, 2015). Licensing is a situation in which a licensor provides a licensee with the permission to make use of their intellectual property (Drozdoff & Fairbairn, 2015). In exchange the licensee usually agrees to make payments to the licensor (e.g. upfront fees, royalties) (Drozdoff & Fairbairn, 2015).

Simple licensing agreements involve a passive collaboration in which knowledge flows are rather unilateral (Martínez-Noya & Narula, 2018). In a cross-licensing contract, each party grants rights to their intellectual property to the other parties involved in the contract.

Frequently, licensing contracts are *"established around relatively early-stage technology, where the path to an ultimate commercial product is not entirely certain"* (Drozdoff & Fairbairn, 2015, 2).

According to Drozdoff and Fairbairn (2015) the object of the license can be used in at least 3 manners:

- To develop new products or services
- To make and sell products or services within a defined geographical area
- To secure exclusivity in a market as an offensive tool to exclude potential competitors from selling the same products or services

Licensing can be exclusive (only one licensee) or non-exclusive (Drozdoff & Fairbairn, 2015). The one licensee benefiting from an exclusive license is sole executant of the rights given in the agreement (Drozdoff & Fairbairn, 2015). For the duration of the agreement the whole ownership of the rights are transferred from the licensor to the licensee (Drozdoff & Fairbairn, 2015). In a non-exclusive licensing agreement the licensor retain the IP rights and can grant them to several parties, each only having permission to use them (Drozdoff & Fairbairn, 2015).

Other non-equity based collaboration agreements such as joint R&D contracts, supplier co-makership contracts and R&D contracts are contractual relationships in which *"parties share resources, expertise, and risk of success or failure depending on their relative contributions"* (Drozdoff & Fairbairn, 2015, 4).

They can range from small-scale individual projects to strategic partnerships with multiple stakeholders (OECD, 2013). Joint R&D contracts are co-funding situations in which research organizations and private companies jointly commit their resources to carry out joint research project (OECD, 2013). R&D contracts (or contract research) are situation in which a private firm commission a research organization to work on a problem of interest (OECD, 2013). R&D contracts are distinct from most types of consulting since they involve the creation of new knowledge (OECD, 2013). Therefore, R&D contracts are not market forms of transactions due to low level of standardization of the request. Supplier co-makership contracts are specific form of R&D contracts with a firm's specialized suppliers rather than research organizations.

Equity-based and contractual joint ventures are *"organizational units created and controlled by two or more parent-companies*" (Hagedoorn, 2002, p. 478).

The difference is on the type of control parent companies have over the joint venture. Hence, the joint venture is equity-based, patent companies bother have shares in the new organization. While only contractual agreements link patent companies in contractual join ventures. From a transaction costs perspective, the first is closer to hierarchy, while the latter is closer to market alliance.

Mergers and acquisitions are used interchangeably or as a combo term. Mergers differ in meaning from acquisition even if at the end of both operations, two companies become one. Mergers is situation in which two companies cease to exist as distinct entities but as the combination of both. Subsequently, they form a new legal entity with a new corporate name. On the contrary, in acquisition deals, one company buys out another one making it its property. This difference is meaningful in terms of managing sharing, since in the case of mergers the initial two companies both have managing shares, while the acquired company is at the level of strategic asset.

In conclusion, BM innovation can be the result of seeking novelty or efficiency (Bohnsack et al., 2014). From the perspective of transaction costs economic, efficiency focus on cost reduction of existing transactions and novelty correspond to new way of handling transactions (Bohnsack et al., 2014). Cost reduction and enhancing value are considerations that drive firms to undertake collaborations (Martínez-Noya & Narula, 2018). Both the economic and strategic management approaches provide sound explanation of the increasing trend in knowledge intensive industries to collaborate (Martínez-Noya & Narula, 2018).

In Table 1, the main motivation to form collaborations are explored from both the economic perspective of transaction costs theory and strategic management perspective such as the theory of resource dependence (Martínez-Noya & Narula, 2018).

Table 1. Motivation to form collaborations (Source: Adapted from Martínez-Noya & Narula, 2018; Hagedoorn et al., 2000)

Transaction costs perspective	**Strategic management perspectives**
- Minimize costs of transactions involving intangible assets (technical knowledge) - Circumvent incomplete contracts - Avoid opportunistic market behavior - Avoid high costs of internalizing the activity	- Share R&D costs / Pool risks - Economies of scale and scope - Co-opt competition - Improve competitive position - Coordinate value chains with coalition partners - Increase efficiency, synergy, power through network - Access complementary resources to exploit own resources - Use collaboration as learning vehicle to accumulate and deploy ne skills and capabilities - Learn from partners, transfer technology - Create new investment options

The pharmaceutical industry offers an ideal context to study BM innovation for the accommodation of potentially disruptive technologies. The current pharmaceutical industry was established in the interwar years (20th century) with the advent of insulin and penicillin (pharmaphorum, 2020). The industry's seeds trace back to the end of the 19th century, when some apothecaries (e.g., Merck KGaA) or fine chemicals businesses (e.g., Pfizer) started exclusively manufacturing medicines such as painkillers and antiseptics in bigger scales. Hence, a BM innovation, based on economies of scale and standardization of drugs' batch to batch production, is the corner stone that led small pharmacies and chemical firms to become the giant Big Pharma companies of today. Many scholars and practitioners agree that the BM design of Big Pharma firms tremendously changed since the early 1980s (e.g. Downs & Velamuri, 2016, pharmaphorum, 2020, Pwc, 2009, Clough, 2002). The BM changes happened simultaneously to the advent of biotechnologies in the industry, even if causality between the two events is insufficiently demonstrated (Clough, 2002).

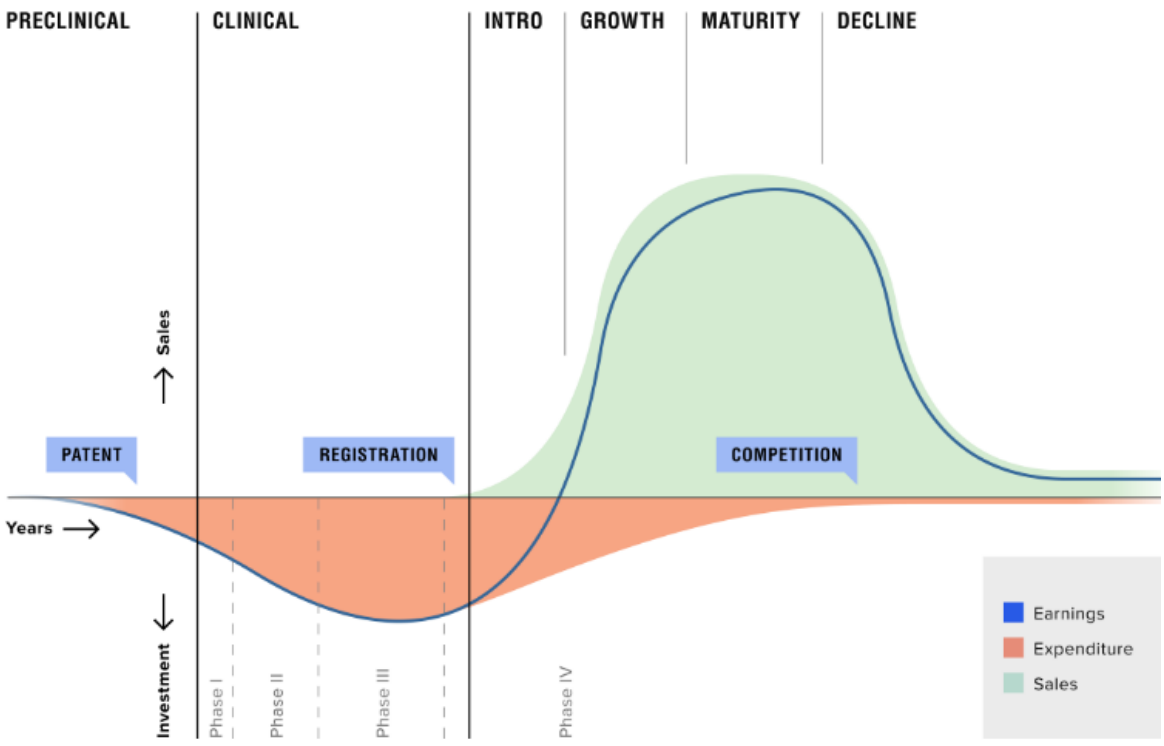
Before starting with the description of the old and new BMs of Big Pharma firms, in the following chapter, the pharmaceutical market, the life cycle of a drugs and the Big Pharma firms are presented.

2.5. Pharmaceutical market and drugs life cycle

The pharmaceutical industry consists of a network of companies that ensure the discovery, development, production, distribution, and marketing of drugs (McGuire et al., 2010). Drugs, medicines or medicinal products are any substance or their combination that is intended to treat or prevent a human disease, or by means of pharmacological, immunological or metabolic action, to restore, correct or modify physiological functions or diagnose a disease (Directive 2001/83/EC, 2001). According to this definition, other medical products such as vitamins or medical devices are not considered drugs. The focus of thesis is only on drugs for human use.

The five stages view of Kotler et al. (2013) to describe a drugs' life cycle is adopted. Product development is the first stage of a drug's life cycle (Kotler et al., 2013), followed by introduction, growth, maturity and decline as defined by Levitt (1965) (see Figure 8).

Figure 8. Drug life cycle (Source: van der Gronde et al., 2017)



In fact, a drug is made of substance(s) having medicinal properties (active pharmaceutical ingredient (API)) and other substances without medicinal properties but that are necessary for the drug formulation (excipients).

The drug development stage consists of research on new substance(s) having medicinal properties and development of new drug, its regulatory registration (Gollin, 2001) and market access negotiations. After conducting basic and applied research to demonstrate the medicinal properties of potential new APIs, the development of a new drug starts with preclinical studies (e.g. animal models, in vitro tests) (Gollin, 2001). Preclinical studies aim to support the clinical trials for instance by identifying lead candidates from several possible drugs, or the best drug formulation (Steinmetz & Spack, 2009). Typically, during the preclinical studies patents for more than one promising API are filed (Gollin, 2001). The drug formula is not patentable and kept secret. Drug candidates will go through the three phases of clinical trials. The drug development process lasts on average 10 to 15 years (Sorrentino & Garraffo, 2012), which are subtracted from 20 years of exclusivity rights of the patent (Gollin, 2001). Then, all drugs need to have a valid so-called marketing authorization to be allowed to be on the market. This step is the regulatory registration of a new drug. The decision to grant a drug with a marketing authorization is mainly informed by safety, efficacy and quality outcomes reported from clinical trials (Nuijten, 2014). Finally, the market access step consists of negotiations with health authorities (except USA) to define reference prices and reimbursement status of new drugs (van der Gronde et al., 2017). The effective access of drugs to market depends on the market access step rather than regulatory registration step. For most drugs, the product life cycle curve starts with high investments in the drug development phase, then sales take off after market access and decline with patent expiration and increased competition (van der Gronde et al., 2017). Because drugs only benefit from patents protection during the first years of commercialization, Big Pharma need to fill up their product portfolio with new innovative drugs rapidly to remain competitive and profitable.

Drugs on the market can be divided into prescription drugs and over-the-counter (OTC) drugs (U.S: Food and Drug Administration, 2017). Consumers can order OTC drugs for themselves, without needing a physician's prescription, and they can buy them from pharmacies directly (or from off-the-shelf in stores in USA) (U.S: Food and Drug Administration, 2017). On the other hand, the commercialization of prescription drugs is highly regulated (Sabatier et al., 2010).

Prescription drugs require a physician prescription to a specific patient and is procured in a community pharmacy (U.S: Food and Drug Administration, 2017).

The market for prescription drugs is not truly a free market since "*in free markets, a consumer decides on, buys, pays for and uses a product*" (van der Gronde et al., 2017, p. 13). An additional difference between OTC and prescription drugs concerns the rules for advertising. For prescription drugs, direct-to-consumer advertising is illegal in most countries (except USA and New Zealand) (van der Gronde et al., 2017). Companies commercializing prescription drugs can conduct scientific communication activities (marketing activities) with health professionals only. The focus of this paper is on the commercialization of prescription drugs by Big Pharma firms. Big Pharma firms are for-profit and large and mature multinational firms that have the capabilities and assets for developing, manufacturing, and distributing innovative products or so-called 'brand name drugs' (Cockburn, 2004; Mehraliana et al., 2012; Tangour et al., 2019), such as Merck, Johnson & Johnson, Pfizer, Bristol-Myers Squibb, Abbott Labs and Eli Lilly (Gottinger & Umali, 2008). Many of them trace their roots in the nineteenth century and were first involved in the chemical industry (Cockburn, 2004) such as Pfizer (founded in 1849) (Rebecca, 2010).

Big Pharma firms are firms that in 2019 or 2020 had more than 10 billion (EUR or USD or GBP) in revenues or turnover. A distinction can be made between traditional Big Pharma companies and recent Big Pharma companies. Unless specified, in this thesis the mention of Big Pharma firms alone refers to traditional Big Pharma companies and not the recent ones.

Traditional Big Pharma companies were already established at least 20 years before the defined date of the advent of biotechnologies in the industry (1980s). Table 2 provides an overview of traditional Big Pharma companies.

Table 2. List of traditional Big Pharma firms (Source: Own table [i])

Company name	Founded on	Head-quarter	Annual revenues (R) / turnovers (T)
Abbott Laboratories	1888	USA	34.6 billion USD (R/2020)
AstraZeneca	1913*	UK	26.6 billion USD (R/2020)
Bayer	1863	Germany	41.4 billion EUR (T/2020)
Boehringer Ingelheim	1885	Germany	19 billion EUR (R/2019)
Bristol-Myers Squibb	1887	USA	39.3 billion USD (R/2020)
Eli Lilly & Co	1876	USA	22.3 billion USD (R/2019)
GlaxoSmithKline (GSK)	1848*	UK	34 billion GBP (R/2020)
Johnson & Johnson (Jansen)	1886	USA	82.584 billion USD (R/2020
Merck & Co. (MSD)	1891	USA	47.9 billion USD (R/2020)
Merck Group (Merck KGaA)	1668	Germany	17.5 billion EUR (R/2020)
Novartis	1857*	Switzerland	48.6 billion USD (R/2020)
Novo Nordisk	1923	Denmark	16.4 billion EUR (R/2019)
Pfizer	1849	USA	41.9 billion USD (T/2020)
Roche	1896	Switzerland	64.7 billion USD (2020)
Sanofi	1947*	France	36 billion EUR (2020)
Takeda Pharmaceutical	1781	Japan	30.3 billion USD (2020)
Teva Pharmaceutical Industries	1935	Israel	16.8 billion USD (2019)

(*) is the foundation date of the oldest of the companies being merged.

Certain DBFs which were founded around the turning point of 1980s, succeed in becoming recent Big Pharma companies such as the companies listed in Table 3.

Table 3. List of recent Big Pharma firms (Source: Own table [ii])

Company name	Founded on	Head-quarter	Annual revenues
Abbvie	2013	USA	45.8 billion USD (2020)
Allergan plc	1983	Ireland	16.1 billion USD (2019)
Amgen	1980	USA	25.4 billion USD (2020)
Biogen Idec	1978	USA	14.4 billion USD (2019)
Gilead Sciences	1987	USA	22.5 billion USD (2019)

At the end of the 21st century, Big Pharma companies' biggest fear, which is a combination of severe revenue losses and empty product pipelines, became a reality. When biotechnologies emerged, an opportunity to create growth through new products lines rose. However, biotechnologies represent a technological discontinuity from the conventional organic chemistry, especially in their discovery and development approaches (Anand et al., 2010). It was new entrants to the pharmaceutical industry, DBFs that were the first to commercialize these biotechnologies through innovative BMs. Big Pharma firms still succeeded in commercializing biotechnology-based drugs mainly through their collaborations with DBFs. Big Pharma firms showed that DBFs did not represent a real threat to their businesses and that the challenges associated with the emergence of biotechnologies were to design of a fitting BM innovation. Drozdoff and Fairbairn (2015) argue that when it comes to biotechnologies, Big Pharma companies increasingly prefer academic–industry partnerships for conducting foundational research to garnish their drug discovery pipelines. They are investing several millions in many large-scale, multiyear collaborations with academia in drug discovery deals (Drozdoff & Fairbairn, 2015). Other authors report the many acquisitions of small and medium sized dedicated biotechnologies firms by Big Pharma firms (Downs & Velamuri, 2016; Greiner & Ang, 2012; Martínez-Noya & Narula, 2018). It was also reported that Big Pharma firms experienced an era of big mergers during the same period (Birkinshaw et al., 2018).

R&D collaborations are but one activity for creating value. The literature remains discreet on how other activities to create value, such as manufacturing, or marketing are affected by the pursuit of biotechnologies. Finally, what exactly are new value positions brought by biotechnologies? In the following chapter, BM designs of Big Pharma firms before and after the advent of biotechnologies are conceptually derived from the existing scientific literature.

3. Conceptually Derived Business Models of Big Pharmaceutical Firms

In this chapter, a systematic literature review on BM research in the pharmaceutical industry is conducted. The aim is to describe BMs of Big Pharma firms before and after the advent of biotechnologies. A secondary aim is to describe the trend of biotechnologies from a business perceptive as well as other concomitant trends that influence the design of Big Pharma firms' BM innovation. In the following, the methodology is first described followed by the results.

3.1. Methodology: Systematic literature review

3.1.1. Data identification and collection: Systematic literature review

Literature reviews are fundamental to academic research. Okoli and Schabram (2010, pp. 2–3) distinguishes between three categories of literature reviews, namely *"literature reviews as theoretical foundation for primary research", "stand-alone literature reviews"* and *"literature reviews for graduate student theses"*. According to the three category a literature review can (Okoli & Schabram, 2010):

- Aim to provide a theoretical foundation to a main study such as by introducing relevant concepts, specific vocabulary, and key variables.
- Serve as an anchoring point to an academic deliverable such as a thesis. It demonstrates the student's ability to synthetize previous knowledge and to integrate most influential researchers' contributions.
- Be themselves a distinct research pursuit. They are valuable for policy development and supporting the practice.

Systematic literature reviews are different from traditional narrative or non-systematic reviews of the literature (Booth et al., 2016; Bryman & Bell, 2015; Tranfield et al., 2003). Reviews of the literature are systematic when they are a "*replicable, scientific and transparent process… that aims to minimize bias through exhaustive literature searches of published… studies and by providing an audit trail of the reviewer's decisions, procedures and conclusions*" (Tranfield et al., 2003, p. 209).

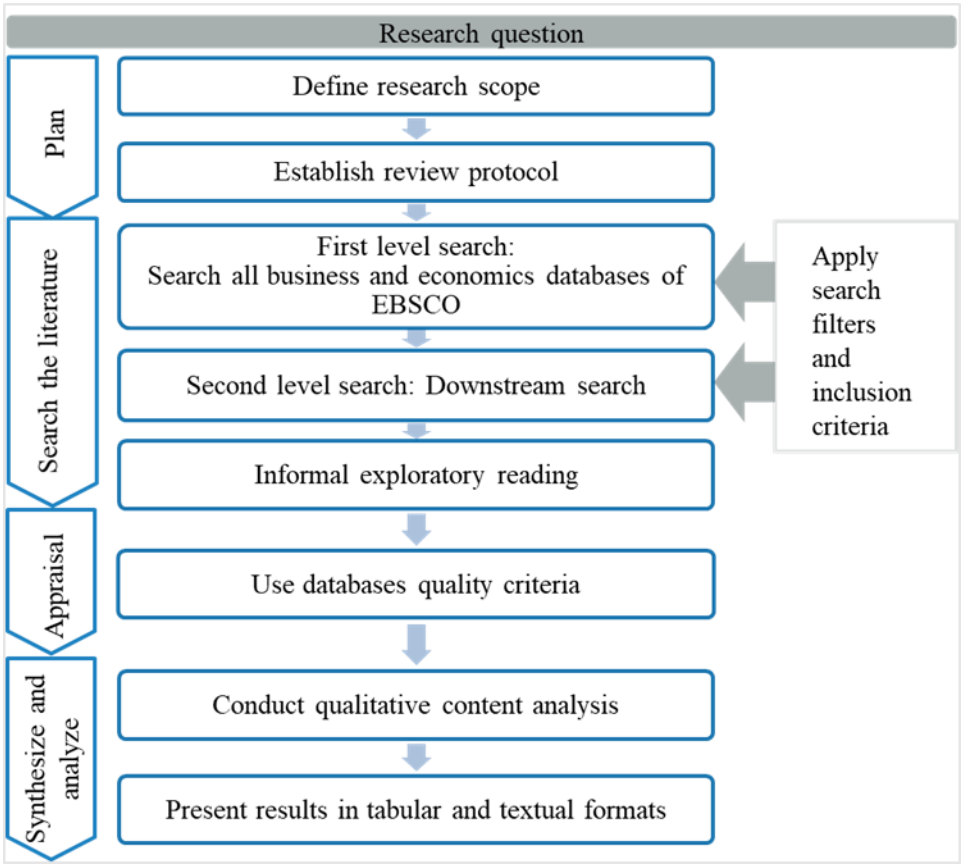
A systematic literature review that stands alone, aims to *"identify new ways to interpret, and shed light on gaps in previous research"* (Booth et al., 2016, p. 14).

At least three types of research questions are most suitable for systematic literature reviews, namely "*effectiveness questions", methodology questions"* and "*conceptual questions"* (Booth et al., 2016, p. 13). While effectiveness questions focus on the comparable effects of interventions (often medical), methodology questions research focus on use, strengths, and weaknesses of methods. Conceptual research questions asks how a certain phenomenon has been identified and defined (Booth et al., 2016).

Additionally, systematic literature review can differ on the degree to which they are systematic and on the type of studies included (i.e. qualitative and/or qualitative studies) (Booth et al., 2016). Consequently, there are many types of systematic literature reviews such as mapping review, scoping review, and meta-analysis just to cite a few. A so-called *integrative review* that is a deep analysis of the literature is conducted. This type of systematic literature review is also conducted by Downs and Velamuri (2016) and van der Gronde et al. (2017). According to Booth et al. (2016, p. 24) an integrative review includes *"both experimental and non-experimental research in order to understand more fully a phenomenon of concern"*. It consists of an *"exhaustive search to identify maximum number of eligible primary sources using two or more strategies"* for the literature search (Booth et al., 2016, p. 24). Results of integrative reviews are often synthesized in tabular form *"usually according to a framework"* and the critical analysis of data displayed is "*key to comparison and identification of important patterns and themes" (Booth et al., 2016, p. 24).* The integrative systemic literature review is best suited to locate, evaluate and recombine pieces of information (Booth et al., 2016) from the existing body of literature on BMs in the pharmaceutical industry.

This research methodology is based largely on the guidance of Booth et al. (2016) on how to conduct a systematic literature review. They introduce the SALSA framework (for Search, Appraisal, Synthesis and Analysis) (Booth et al., 2016). SALSA framework represents the key elements of the review process (Booth et al., 2016). As shown in Figure 9, the process of systematic literature review consisting of: Searching the literature, its quality appraisal, synthesizing and analyzing studies and the presentation of review results. This approach was selected since it provides useful tools and a detailed steps of a systematic literature review, which were missing from the methodological inputs described by Bryman and Bell (2015) and Tranfield et al. (2003).

Figure 9. Process of systematic literature review (Source: own figure based on Booth et al., 2016)



The planning phase consists in defining the scope of the research and establishing a review protocol. The protocol outlines the whole review process, aims to protect the research against bias and keeps it on track (Booth et al., 2016). In the protocol, the aim and scope of the research, review questions, predefined search parameters and review steps are noted. Clearly-defined review questions are important to inform inclusion criteria (Booth et al., 2016). The review questions guiding this literature search are the following: What is the traditional BM of Big Pharma firms? What are the changes that occurred in the industry during the biotechnology revolution? How do Big Pharma firms create, deliver, and capture value out of biotechnology-based prescription drugs?

Conformably to the suggestion of Booth et al. (2016) to conduct an exhaustive search, two search levels are defined to ensure a comprehensive capture of relevant articles. The first level search consists in a systematic search of suitable databases. All business and economics databases provided by EBSCO are searched, which include Business Source Complete, Regional Business News, SPORTDiscus, SPORTDiscus with Full Text, EconLit with Full Text, and eBook Collection (EBSCOhost).

EBSCO Business Source Complete database includes more than 1300 business journals (EBSCO Information Services, 2020) and is considered one of the largest databases for management science (Downs & Velamuri, 2016; Zott et al., 2011). There are no relevant studies in medical databases (e.g., PubMed) which focus on purely biomedical studies, which is why they were not searched. The EBSCO database employs strict quality assessment criteria for the inclusion of journals. By limiting the search to this database, its quality criteria are used as a proxy to waive the need to conduct further quality appraisal of the included publications. There are no relevant studies in medical databases (e.g., PubMed) which focus on purely biomedical studies, which are not the focus of the thesis.

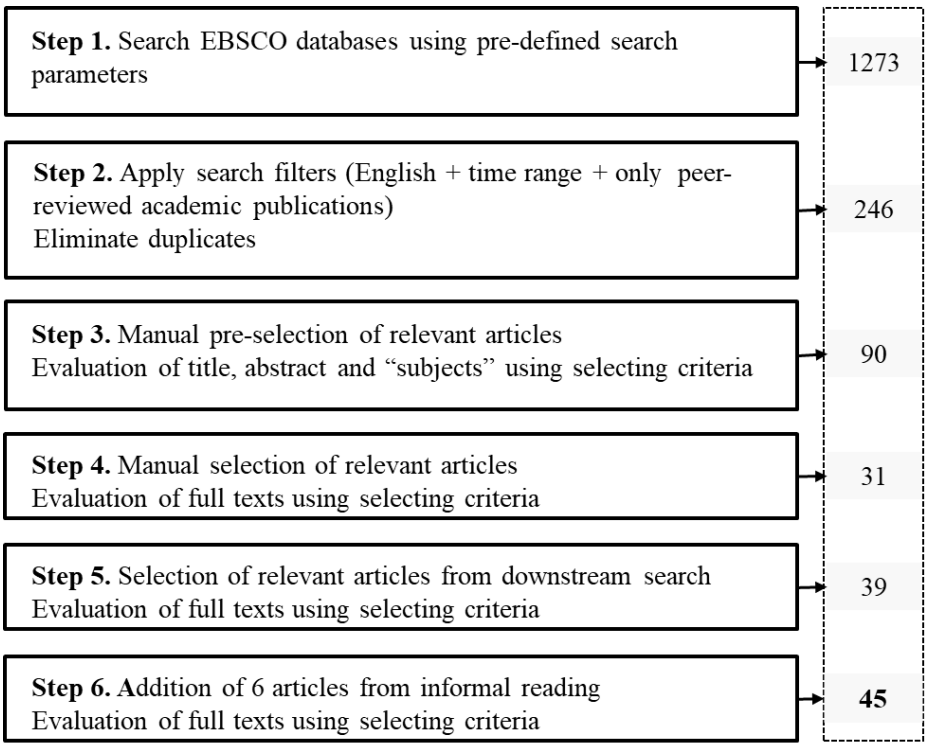
The scope of the literature to be searched is limited to peer-reviewed academic publications in English published from 1976 to March 2020 (search filters). This starting year corresponds to the founding year of Genentech (Downs & Velamuri, 2016), which signed the beginning of the biotechnologies revolution (Horvath et al., 2019). Since a unified BM definition is missing and there are many perspectives on the subject (see 2.2.), a variety of terms were associated with the concept of BM. The review questions span the boundaries of Big Pharma firms (i.e., industry trends), which is why "pharmaceutical industry" was used as a search term. Similarly, the varying terminologies referring to the pharmaceutical industry is an issue. This explains the wide range of associated terms selected for the search parameters. All papers not focusing on the natural science research field of biotechnology are excluded by applying the Boolean operator "NOT". The search parameters used can be found in Appendix 1.

The search, before applying any filters, results in 1273 articles. By applying search filters and the removal of duplicates, an overall sample of 246 articles is obtained. The articles to be included are always evaluated according to the following inclusion criteria, adapted from Zott et al. (2011) and Downs and Velamuri (2016):

- Deals with BM concept, as defined in this thesis, in a non-marginal way. Papers in which the concept of BM only makes a marginal part of their contribution such as only mentioned in the introduction or conclusion are excluded.
- Deals specifically with pharmaceutical industry in a non-marginal way. Papers that focus on non-pharmaceutical industries such as hospitals or the agro-food industry are excluded.

The selection is conducted in two phases: a preselection and final selection. The preselection phase aims to sort out papers that are clearly dealing with other themes than the focus of the research such as process modelling, investment models, supply chain optimization, or nanotechnology. During this phase, the title, abstract and "subjects" (as defined by EBSCO) of the 246 sampled articles are reviewed based on the selection criteria. Consequently, 90 articles are preselected. The final selection follows a full text review. The full-texts review determines whether papers' perspectives on the BM concept fits the working definition of this thesis and if BMs are at the center of their findings. For instance, papers that are excluded in this step are focusing on technological innovation, new product development, investments models rather than on BM. As a result, 31 articles are selected. The second level search aims to mitigate any limitations from the first level search strategy such as unforeseen limitations inherent to the EBSCO databases. The second level search consist of downstream search of bibliographic references of selected articles and stochastically discovered publications. The additional publications are selected based on the same selection criteria than above. Finally, 8 articles are added from the downstream search and 6 from informal exploratory reading. The final set of selected articles sums up to 45 articles. The list of selected papers can be found in Appendix 2. Figure 10 presents an overview of the search strategy and the selection process.

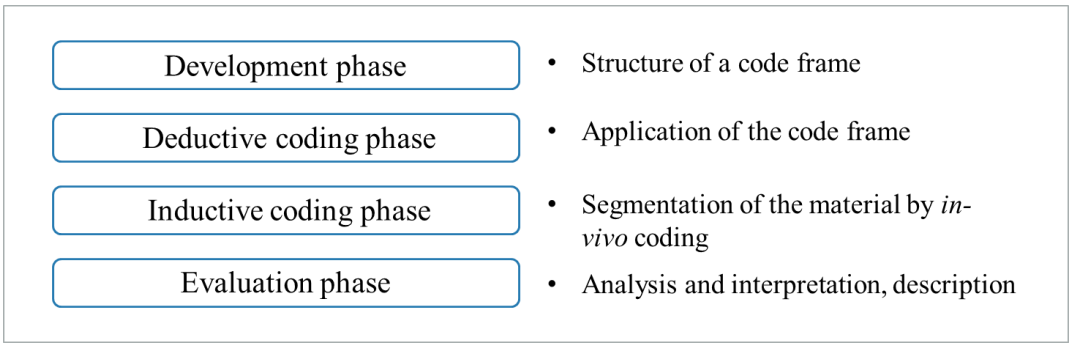
Figure 10. Literature search and selection process (Source: own figure)



3.1.2. Data analysis

The selected articles are analyzed and synthesized following the method of qualitative content analysis. This research method allows researchers to examine qualitative data in a replicable and systematic manner (Bryman & Bell, 2015). Kuckartz (2014, 2016, 2019), Mayring (2015, 2016, 2019) and Schreier (2014; Schreier et al., 2019) are the most influential researcher for the method of qualitative content analysis (see 4.1.2). An adaptation of the general steps as described by Schreier (2014) and Kuckartz (2014) (see Figure 11) is used for the qualitative content analysis of the 45 selected papers .

Figure 11. Qualitative content analysis steps (Source: Own figure based on Kuckartz, 2014; Schreier, 2014 Mayring, 2015)

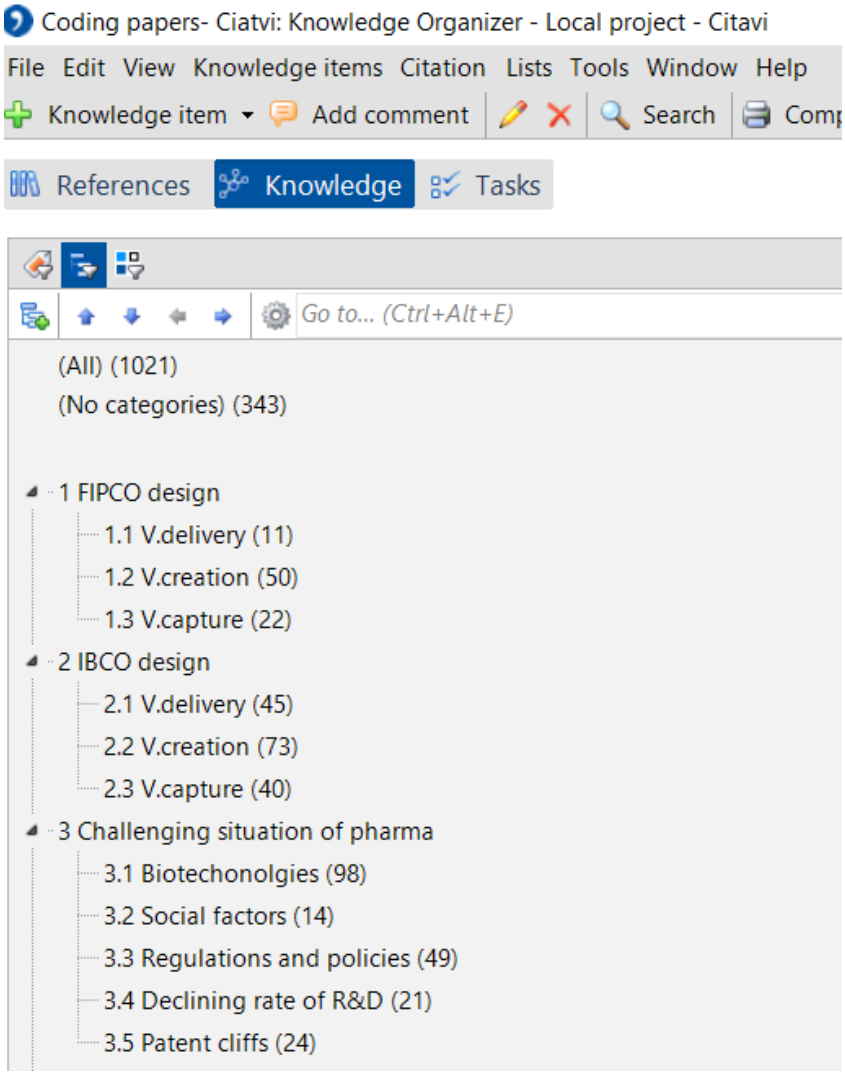


The full texts of the selected papers are downloaded in a PDF format and imported to a dedicated Citavi project. The use Citavi for the qualitative content analysis of the selected papers is preferred to other software packages. Citavi is a reference management software that can also be used to code text segments by using the functions of direct citation and the management of citation in the knowledge organizer space. Full texts are read directly in Citavi, and text segments are selected and marked as direct citations. Direct citations are, then, attributed to a specific knowledge category or code. In the knowledge organizer space in Citavi, categories can be organized heretically to build a coding frame (see Figure 12).

The selected papers are coded using a combination of deductive and inductive approaches. The papers are first coded deductively following a chronological logic. The same deductive coding system is used once to capture elements of the traditional BM of Big Pharma firms and then the new BM elements.

The coding system for BM designs consists of the three value-dimensions of the BM working definition: (1) Value delivery (value proposition and customer segments & relationships), (2) value creation (key activities and key partners), and (3) value capture (cost structure and revenue streams).

Figure 12. Screen shot of the coding frame in Citavi (Source: Own figure)



Results from the review are presented in tabular and in textual forms in the next section.

3.2. Results: Conceptually derived Big Pharma firm's business models and key trends in the pharmaceutical industry

The results give a historical perspective on the pharmaceutical industry through two lenses: the lens of business models and the one of key trends affecting the pharmaceutical environment. In summary, this section consists of the description of:

- The pharmaceutical environment before and after the 1980s.
- The traditional BM of Big Pharma firms, often called Blockbuster BM or Fully Integrated Pharmaceutical Companies model (FIPCO).
- The BM of Big Pharma firms since the biotechnologies' revolution: Integrated Biopharmaceutical Companies model (IBCO).

3.2.1. First pharmaceutical era (before the 1980s): Chemical heuristics of drug development

The burgeoning pharmaceutical firms of the 19th century grew by following a heuristic of extraction of API from plants (small organic molecules). For instance, Merck KGaA, a 350-years old pharmaceutical company started as community pharmacy "Engel-Apotheke" in Darmstadt in the 17th century. A heuristic of biologic extraction coexisted with one of chemical extraction, before the establishment of drug making as an industry. Biological heuristic of extraction means that APIs are directly extracted from animals such as anti-toxins serums, adrenaline and insulin (Hopkins et al., 2007).

The establishment of the synthetic chemistry heuristic led to the creation of the pharmaceutical industry. For instance, it is only in 1827 that the pharmacy ""Engel-Apotheke" transformed into a research-based industrial company when Emanuel Merck managed to prepare pure alkaloids (Merck KGaA). Then, synthetic organic chemistry is established as a method to avoid higher costs of chemical extraction process and improve the performance of natural APIs, leading to the development of new fully synthetic APIs (e.g. aspirin) (Hopkins et al., 2007). The heuristic develop to one of "trial and error" of synthetic organic chemistry which is a *"random screening of synthetic compounds characterized as 'molecular roulette'"* (Hopkins et al., 2007, p. 568). With the organic chemistry synthesis of new APIs, Big Pharma experience a gold age of high R&D productivity in the 1950s with a plethora of new products such as antibiotics, steroids and anti-inflammatory drugs (Hopkins et al., 2007).

The early 60s see the decline in productivity of Big Pharma firms and show the limits of the *"molecular roulette'"* logic (Hopkins et al., 2007, p. 568). A third chemical heuristic of targeted screening improves the R&D productivity by synthesizing APIs that were better fitting their protein receptors in the human body. Big Pharma firms, focusing on biochemistry and pharmacology, generate new knowledge on structural characteristics of protein and interactions between APIs and their targets as well as new protein targets by better understanding diseases pathways (Hopkins et al., 2007). This new focus on biology is a mean to extend the value of synthetic chemical heuristics of Big Pharma firms.

3.2.2. Big Pharma firms' business model before the 1980s: Fully Integrated Pharmaceutical Company (FIPCO)

The pharmaceutical industry was established in the late nineteenth century, by Big Pharma firms (Song, 2017, p. 844) and remained stable for over 100 years (Downs & Velamuri, 2016, p. 20). Big Pharma firms drive their competitive advantage from their ability "*to effectively manage product market interactions with regulators and end users and to "fill the pipeline" with internally developed blockbuster drugs"* (Cockburn, 2004, p. 14). This strong belief that product novelty is the best source of competitive advantage in this industry, is reflected in the design of the century-stable BM of the Big Pharma firms, called FIPCO (see Table 4). Incidentally, FIPCO is an abbreviation for Fully Integrated Pharmaceutical Company, which should rather refer to firms rather than their business model, but which is used in the literature instead to refer to the traditional business model of these type of firms (e.g., Boni, 2019; Downs & Velamuri, 2016). The FIPCO overwhelmingly dominated the industry (Cockburn, 2004; Downs & Velamuri, 2016, p. 20; Nicol et al., 2013).

Table 4.Before the 1980s: the FIPCO (Source: Own table)

Business model dimensions		**FIPCO**	**Exemplary citation**
Value Delivery	**Value propositions**	Chemical drugs frequently in pills One-size-fits-all value of drugs/ Mass markets	*"the pill was established as a convenient way to administer a standardized drug dose" (Hopkins et al., 2007, p. 568)*
	Customer segments & relationships	Payers: Automatic reimbursement of drugs Physician: Sampling and detailing model Patients	"*Once a drug was licensed in a country, it was often automatically reimbursable*" (Nuijten, 2014, p. 34)
Value Creation	**Key activities**	In-house drug discovery and development In-house marketing, regulatory affairs Multi-locations manufacturing and global distribution network	*"a 'golden age' of productivity driven by random screening of synthetic compounds characterized as 'molecular roulette'"(Hopkins et al., 2007, p. 568)* *"manufacturer-centric drug discovery"(Song, 2017, p. 843)*
	Key partners	Not mentioned	
Value Capture	**Revenue streams**	Selling drugs	"*old business model based on blockbuster drugs*" (Segers, 2017, p. 16)
	Cost structure	Drug development (until marketing authorization)	"*take the drug through the expensive FDA approval process*" (Abramawicz, 2011, p. 1369)

3.2.2.1. FIPCO's value propositions

In the FIPCO, the Big Pharma companies offer drugs based on Active Pharmaceutical Ingredients (APIs) that are small organic molecules (Boni, 2018). A one-size-fit-all approach is followed to define the value of drugs. They are intended to be prescribed for diseases with high prevalence and subsequently large target populations (mass market drugs) (Song, 2017, p. 844). For example, Paracetamol, one of the most used drugs in the world, has a wide range of clinical indications from pain management of a common cold (and fever) until cancer pain (Prescott, 2000). It was first used clinically in 1893 and only appeared commercially in the USA as of 1950 (Prescott, 2000).

The API paracetamol can be found in many brand-name drugs such as Panadol, which was first marketed by Sterling-Winthrop Co. in 1953 (today by GlaxoSmithKline (GSK)). Since the establishment of synthetic chemistry by Big Pharma firms, the pill became the reference form to conveniently administer a standardized dose of a drug (Hopkins et al., 2007). Oral administration of drugs avoids the need for injection or other roots to make drugs available in the body. The pill adds value to APIs' properties thanks to their simplicity of production, transport, storage, and use.

3.2.2.2. FIPCO's customer segments & relationships

For Big Pharma firms, which commercialize prescription drugs, target customers are threefold. The reason is that prescription drug markets are not truly free since a different entity "*decides on, buys, pays for and uses a product"* (van der Gronde et al., 2017, p. 13). First the physician prescribes a drug and makes the decision of choosing the treatment (van der Gronde et al., 2017). The patient decides whether to execute that "order" (van der Gronde et al., 2017). The insurance company or a government agency (the payer) decides whether to pay for that "order" (van der Gronde et al., 2017). Before biotechnologies, the involvement of patients and payers in a drug's purchase decision was overshadowed by the one of physicians. Payers granted automatically a reimbursement status to a drug holding a marketing authorization, making it immediately *"available for the potential population of eligible patients"* (Nuijten, 2014, p. 34). The criteria of safety, efficiency and quality outcomes required for granting a marketing authorization were sufficient to inform the reimbursement decision (Nuijten, 2014, p. 34).

Until the biotechnologies revolution, "*physicians faced few restrictions on their prescribing behavior from healthcare authorities or other stakeholders within the healthcare system. If physicians were convinced of the clinical benefit of a new medication, they could start prescribing it*" (Nuijten, 2014, p. 34). Consequently, physicians have effectively most of the power over treatment decisions and a real effect on drugs' market shares. Physician offices represent the most important points of product purchase decisions, by means of the "traditional sampling / detailing driven model" (Rao, 2010, p. 207).

3.2.2.3. FIPCO's key activities

The FIPCO (Fully Integrated Pharmaceutical Company), as the name suggests, is a BM where most of the activities for drug production and commercialization are vertically integrated (Downs & Velamuri, 2016; Kohut, 2019; Konde, 2009). Drug discovery, clinical development, regulatory affairs, manufacturing and marketing activities are conducted within the sole boundaries of each Big Pharma firm (Cockburn, 2004). Key reasons were the advantages created by accumulating and containing knowledge in-house to generate knowledge spill-overs across therapeutic areas and strong economies of scope (Cockburn, 2004; Diestre & Rajagopalan, 2012; Downs & Velamuri, 2016). This fully integrated model means that a firm pursues value creation to its utmost level (Konde, 2009). The logic was that by creating as much of the value as possible a firm might capture as large a portion as possible of the value created. Big Pharma firms' key activity is in-house R&D. They approached R&D of chemical drugs from a "stochastic trial and error" approach of large-scale random screening based on organic chemistry (Downs & Velamuri, 2016, pp. 45–46; Hopkins et al., 2007). These R&D activities only required a limited and superficial knowledge of fundamental physiological processes (Cockburn, 2004). Outcomes of drug discovery and development activities, relying on serendipity, are uncertain and have low success rates. Approval rates for new chemical entities averaged 19% (DiMasi et al., 1991). In general, only one out of 6000 synthesized compounds ends up in an approved drug (Sorrentino & Garraffo, 2012).

The main asset of a Big Pharma firm is deriving from its internal and subsequent cash flow that translates, for instance, into multi-locations manufacturing and global distribution network (Cockburn, 2004; Mehraliana et al., 2012). By leveraging advantages of economies of scale (Cockburn, 2004; Downs & Velamuri, 2016), Big Pharma firms are quite performant in the regulatory affairs, manufacturing and marketing activities. They establish global manufacturing facilities worldwide and gain deep knowledge about regulatory requirements in an impressive list of countries making them both very capable and efficient in bringing drugs to the market. Big Pharma firms had limited interactions with external researchers (Downs & Velamuri, 2016, p. 47) since they largely acquired new knowledge *"'for free' by reading journals and attending conferences or by purchasing tangible inputs and services such as scientific instruments or highly skilled graduates"* (Cockburn, 2004, pp. 13–14).

Big Pharma firms purchased licenses of already approved drugs (or in the last clinical trials) to either maintain efficient usage levels of their marketing and manufacturing assets or to get access to local knowledge, regulators and distribution channels in the international context (Cockburn, 2004, pp. 13–14). No mention of key partners has been found in the selected papers.

3.2.2.4. FIPCO's revenue streams and cost structure

In 1987, a typical new chemical drug cost around $114 million (1987 dollars) until marketing authorization was granted (DiMasi et al., 1991), which would be worth about $280 million in 2022 dollars[iii]. The long time-lag between investment and revenues, and the high risks attributed to R&D outcomes are specific financial attributes of the pharmaceutical industry (Sabatier et al., 2010). An average a Big Pharma firm spends about 14 to 15 % of its total revenues on R&D (Downs & Velamuri, 2016, p. 20) and even more on marketing (van der Gronde et al., 2017). The return on investments for Big Pharma firms is highly skewed (due to R&D characteristics) and is on average *"modestly above cost-of-capital"* (Grabowski et al., 2002, p. 11). Interestingly the pricing for new drugs is not related to customers' valuation of these products (van der Gronde et al., 2017).

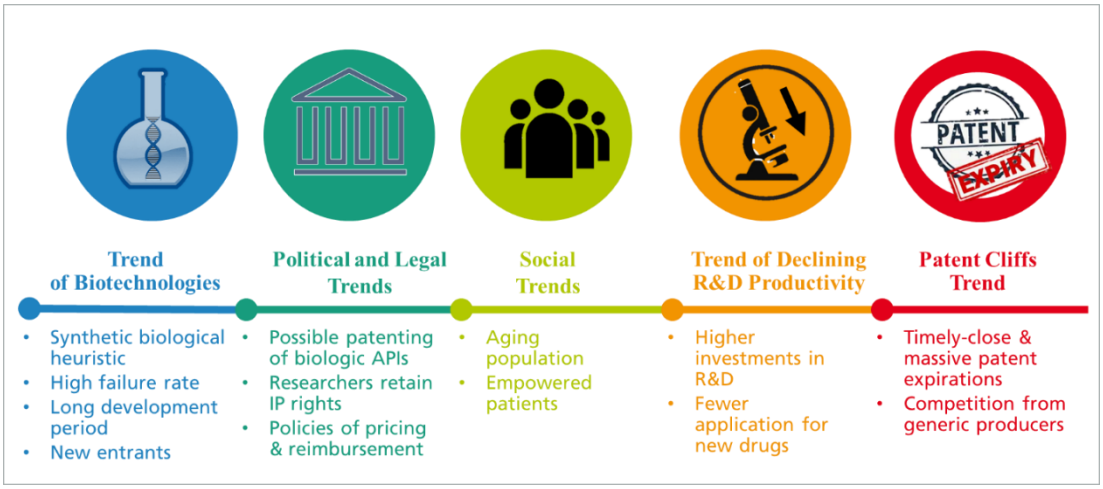
The FIPCO is also called "Blockbuster Drug" BM (Boni, 2018). The blockbuster model builds on the ability of a company to make the large share of its turnovers based only on one or few highly profitable products with an annual global revenue greater than $1 billion (Boni, 2018). The blockbuster guarantees substantial revenues to the company as long as the patent (or its extension) protecting the API is valid (Boni, 2018). Big Pharma firms capture values generated *"through a combination of extensive patenting, proprietary know-how, brands, regulatory barriers to entry, and favorable product market conditions"* (Cockburn, 2004, p. 13). Patents are of greater importance in the pharmaceutical industry than for other technological sectors (Abramawicz, 2011). The extraordinary costs of drug development and threat from being easily copied by generic drug manufacturers (Abramawicz, 2011) because of the relative simplicity of the small organic molecules protected by these patents, render the exclusivity allowed through the patents fundamental to capturing value from new drugs. It is believed that the removal of the patenting system would virtually lead to the disappearance of the private drug research at the heart of the FIPCO (Abramawicz, 2011).

Big Pharma firms have adopted a highly financed BM (especially in the USA), and they are driven by the *"ideology of maximizing shareholder value"* (Tulum & Lazonick, 2018, p. 282). Stock-price yield and dividend yield are key performance metrics (Tulum & Lazonick, 2018). The top Big Pharma firms have an average profit margin of 16 to 20% (for the top ten pharma companies) (van der Gronde et al., 2017, p. 12).

3.2.3. Second pharmaceutical era (since the 1980s): Biotechnologies and other concomitant pharmaceutical trends

The literature mentions political, technological, and social changes that signal the end of the first pharmaceutical era. These changes begin in the 1980s with the emergence of dedicated biotechnology firms (DBFs) (Boni, 2018; Song, 2017) and continue through the new millennium with the emergence of new policies, demographic changes, lowering of R&D inputs and patent expirations (see Figure 13).

Figure 13. Biotechnologies and other concomitant trends of the pharmaceutical industry (Source: own figure)



Biotechnologies are considered a breaking point in the pharmaceutical history because they introduced the new synthetic biology heuristic. The *"revival of the biological heuristic"* happens when DBFs, leveraging genetic engineering and monoclonal antibodies to study and manipulate living organisms, develop innovative drugs with greater quality (e.g. human insulin) and established a novel heuristic of biological synthesis (Hopkins et al., 2007, p. 569). Equipped with a wide toolbox of biotechnologies (e.g. restriction enzymes and cell culture methods), DBFs provided new operational principles on cutting genes, and expressing the corresponding proteins in germs in scalable volumes (Hopkins et al., 2007).

This allows biotechnology-based drugs to be manufactured more safely and economically as opposite to previous process that produced protein either in very small amounts or through expensive extraction (Hopkins et al., 2007).

3.2.3.1. Trend of biotechnologies

Biotechnologies make a plethora of new product innovations imaginable and possible. The biotechnology science field is vast and encompasses various techniques such a molecular genetics, recombinant DNA and biochemistry (Anand et al., 2010). Biotechnologies intended for medical use are new technologies to study and manipulate living organisms and their compounds (at genetic, protein, cell and tissue levels) to enable commercial medical applications (Kohut, 2019). The Human Genome Project, that was coordinated by the US American National Institutes of Health in the 1980s, is recognized as the leading driver for accelerating the emergence of innovation based on biotechnologies (Gottinger & Umali, 2008). It is only the establishment of Genentech as a dedicated biotechnology firm (DBF) and the successful commercialization of the first biotech-based drug, the synthetic human insulin developed in collaboration with Eli Lilly & Co (Big Pharma), which signed the beginning of biotechnologies as a new trend (Downs & Velamuri, 2016). Biotechnologies are complex and uncertain (Sorrentino & Garraffo, 2012). They have higher attrition rate or risk of failure and require a longer development period (Konde, 2009).

Biotechnologies affect the entire pharmaceutical ecosystem of stakeholders (Downs & Velamuri, 2016; Hopkins et al., 2007)**.** Big Pharma firms started facing an increasing competitive environment (Wenzel et al., 2014, p. 91) with the emergence of DBFs and their protein-based therapies (Boni, 2018). Only a handful of the DBFs sought to compete with Big Pharma firms by leveraging the FIPCO (Boni, 2012; Cockburn, 2004, p. 15). For instance, Amgen and Genentech that built large vertically integrated firms are considered early biotech pioneers (Niosi & McKelvey, 2018; Schmieder & Andrew-Wani, 2014). According to The Wall Street Journal, Genentech registered *"one of the most spectacular market debuts in recent history"* for her Initial Public Offering (IPO) that opened at a price of $35 for each of its million shares and reached $71.25 by the closing time of the stock market (Fraser, 2016).

Biotechnology-based drugs have new modes of synthesis (Anand et al., 2010), requiring micro-organisms to produce big proteins. Biotechnology-based drugs are assembled inside bioreactors that house genetically engineered microbes or specific types of cell cultures. Second they require a new type of knowledge (Anand et al., 2010), which has less to do with the therapeutic properties of the chemicals and more with the biological characteristics of diseases and their pathways. For instance, the development of pharmacogenomics technology facilitates the identification of specific subsets from the whole patient population, who benefit more from the new drug, due to specific genetic trades (Abramawicz, 2011). Certain biotechnology-based drugs are indicated for sub-groups of patients, which constitute niche markets (Song, 2017, p. 848).

3.2.3.2. Political and legal trends

Two main U.S. regulatory decisions set a favorable contingent situation for for-profit entities to appropriate and capture value from the new biotechnologies. First, in 1980, the US Supreme Court decided that patenting is possible for a genetically engineered bacterium (Gottinger & Umali, 2008). This decision allows firms to use the mechanism of patent protection to secure revenues from the development of biologic drugs. Second, the Bayh-Dole Act (Public Law 96-517) is a regulation designed to facilitate the access of small firm to new technologies originating from university research laboratories (Mowery et al., 2001; Tulum & Lazonick, 2018). This legislation open the way for universities to retain patent rights and freely commercialize the results of taxpayer-funded research (Downs & Velamuri, 2016; Tulum & Lazonick, 2018).

Drugs' pricing and reimbursement policies are among the changes that are affecting the pharmaceutical industry since the beginning of the 1980s to this day (Boni, 2018; Capo et al., 2014). Payers, which can be health authorities, public or private insurance companies, decide which new drug to reimburse (include in health insurance packages) (Nuijten, 2014, p. 34). In many countries (except the USA), payers negotiate price of new drugs (van der Gronde et al., 2017). The evaluation of a drug's reimbursement dossier is a new extra step between granting market authorization and access to the market (Nuijten, 2014, p. 35). Thus, *"reimbursement authorities, payers, and new pharmaceutical policies are increasingly determining market entry, future sales, and post-launch costs"*, to manage the funding impact of *"new, premium price, innovative drugs"* (Nuijten, 2014, p. 34).

In recent years, payers' costs of drugs are rising faster than other healthcare products or services. For instance costs for oncology drugs grow at rate of 21% per annum (Adamski et al., 2010). Many payers have become more involved in physicians' perceptions practices, by restricting *"who can prescribe a drug and for which conditions"* (Nuijten, 2014, p. 35).

3.2.3.3. Social trends

In key Western markets demographic changes are happening. Large portions of the population (mostly baby boomers) are currently entering the elderly group age (Downs & Velamuri, 2016). Since the elderly segment is the dominant consumer of healthcare services and products, the increase of their demographic proportions leads to increased healthcare spending. Payers want to have "*affordable drugs for everyone at the lowest possible price, to reduce healthcare spending*" (van der Gronde et al., 2017, p. 9). Increased healthcare costs increase the pressure on pharmaceutical firms to provide products with "*greater marginal innovativeness and at lower prices*" (Downs & Velamuri, 2016, pp. 20–21).

The involvement of patients in their treatment decision is creating a new social factor of relevance for Big Pharma firms. Empowered patients (Song, 2017, p. 848) follow and gather information about existing and up-coming novel therapeutic choices through channels independent of physicians (Rao, 2010, p. 207). Such patients have been empowered by a combination of social networking tools (Rao, 2010, p. 207) enabled by the internet, but also global networking of patient's initiatives and associations.

3.2.3.4. Trend of declining R&D productivity

Many scholars identify the lowering of R&D productivity as a significant challenge facing the pharmaceutical industry (e.g., Boni, 2018; Song, 2017; Wenzel et al., 2014). Downs and Velamuri (2016, p. 20) report that despite the increase in the collective R&D spending over the last 60 years by over 100 times, "*the rate of output of new therapies is declining versus historical productivity levels"*. For instance, the number of Big Pharma firms application for new drugs in the USA were the lowest in 2010 in comparison to the previous 10 years (Downs & Velamuri, 2016). For van der Gronde et al. (2017, p. 8), higher investments in R&D will not bring R&D productivity rates to their historical values, since "*low-hanging fruits have already been harvested"*.

3.2.3.5. Patents expiration trend

In the early 2010s, the industry experienced a so-called patent cliff, where a massive number of Big Pharma firms patents, especially of their blockbuster drugs, expired in relatively short period of time (Debnath et al., 2010; van der Gronde et al., 2017). When the patent of API expires, generic manufactures can develop and sell their own drugs (based on that API) often at a significantly reduced price compared to the original product. The application for a generic drug marketing authorization is also made simpler by health authorities by waiving the need to conduct clinical trials *de novo*. They define other requirements to prove sufficient similarities between the original and generic drug to allow for substitution of the products (i.e. Bioequivalence studies) (Pankaj et al., 2013). The expiration of patents is a major threat (Boni, 2018; Song, 2017; Wenzel et al., 2014) since it leaves Big Pharma firms open to aggressive competition from generic manufacturers. All around the world, healthcare systems have a clear preference for cheaper generic drugs, since pricing system indirectly favor low-cost products (Wrona & Trąpczyński, 2012). Generic drugs can drop the prices of a drug up to 70%, while for biosimilar prices usually only drop by 20-30% (van der Gronde et al., 2017). A drug that is a copy of a biologic drug is called a biosimilar drug rather than a generic drug. The different name comes with different and stricter clinical requirements to prove the similarity of the biosimilar to the original biologic drug. The risk of substitution by biosimilar is expected to be lesser than for chemical drugs, because of the difficulty to copy their complex APIs (van der Gronde et al., 2017).

During a drug's declining phase, Big Pharma firms have many tactics to reduce losses linked to patent expiry and extend their market exclusivity (van der Gronde et al., 2017). Often they outstretch economic benefits of existing drugs, by applying for new marketing authorizations for additional diseases, simultaneously increasing their market size, and their sales volumes, without often leading to reduced price (van der Gronde et al., 2017, p. 11). Oher tactics target the development of new drug's formulations of an API with an expired patent. Reformulation is made by switching the chiral form of the API or combining APIs into a new drug. Big Pharma firms can be granted three more years of market exclusivity resulting from approved reformulation or for new indications (Song & Han, 2016). Some Big Pharma firms succeed in changing their product from prescription drug to over-the-counter (OTC) drugs, or they decide to produce their own auto-generic (van der Gronde et al., 2017).

For instance, the market life of Allegra, an antihistaminic drug developed by Sanofi Aventis, was prolonged, by selling it as an OTC product (Rebière & Mavoori, 2016).

The declining R&D productivity and peak of patent expirations observed in the last decade results in pipelines shrinking (Song, 2017, p. 848). Associated new technological, political, and social trends, and an intensified generic completion put the financial health of Big Pharma firms under stress. The FIPCO, which reflects the chemical synthetic heuristic of the industry is under pressure.

In conclusion, based on the pharmaceutical trends described above, biotechnologies, are potentially disruptive technologies. Disruptive technologies (unlike sustaining technologies) do not improve products in performance attributes historically valued by mainstream markets (Christensen, 1997). Based on the brief history of R&D heuristics development in the pharmaceutical industry (see 3.2.1), biotechnologies represent a potentially disruptive technologies in comparison to the traditional organic chemistry mastered by Big Pharma firms for at least two reasons.

First, disruptive technologies emerge in distant but adjoining industries and slowly move upwards to poach mass customers from the main industry (Christensen, 1997). Biotechnologies emerged in publicly funded research organizations. The emergence of biotechnologies as a commercially viable technology is a direct consequence of the implementation of the Bayh–Dole Act in 1980 (Drozdoff & Fairbairn, 2015). The Act allows institutions such as e.g. universities to own inventions arising from federally sponsored research projects, which led them to commercialize their new technologies (Drozdoff & Fairbairn, 2015). Patenting new biotechnologies and licensing them to companies was the preferred commercialization path of research organizations (Drozdoff & Fairbairn, 2015). For instance, Stanford University's patents of recombinant Deoxyribonucleic acid (DNA) were licensed to over 450 companies and generated more than $250 million USD until their expiration in 1997 (Feldman et al., 2007).

Second, typically incumbent firms are not motivated to pursue disruptive innovations that target smaller markets with expected lower profitability (Christensen, 1997). Anand et al. (2010) and Birkinshaw et al. (2018) confirm that Big Pharma firms did not initiate the commercialization of biotechnologies but rather small DBFs. Biologic drugs target smaller markets and promise lower profits since biotechnologies initially require higher costs for drug discovery and development.

Biologic drugs were problematic for most Big Pharma firms, because of a new knowledge base required for discovering new APIs and drug formulations (Hopkins et al., 2007). The discovery of biotechnologies-based compounds required a deeper and science-intensive knowledge of underpinning physiological phenomena (Cockburn, 2004). In general, Big Pharma firms *"adopted a 'wait and see' approach*", and left DBFs such as Amgen and Genentech to develop the first biological drugs (Hopkins et al., 2007, p. 570).

In the following, the new BM developed by Big Pharma firms which reflects an R&D heuristic of biologic synthesis is presented.

3.2.4. Big Pharms firms' business model since the 1980s: The Integrated Biopharmaceutical Company (IBCO)

When biotechnologies emerged, all Big Pharma firms started from the similar situation of generating revenues from selling chemical drugs and having none to limited capabilities in the emerging technology field (Birkinshaw et al., 2018). The way Big Pharma firms create, deliver, and capture value out of biotechnologies is described in the Integrated Biopharmaceutical Companies (IBCO) model (see Table 5).

Table 5. Since the 1980s: the IBCO (Source: Own table)

Business model dimensions		**IBCO**	**Exemplary citation**
Value Delivery	**Value propositions**	Biotechnology-based drugs: - Distinct therapeutic value - Targeted patients sub-groups / Niche markets	"*Diseases that seemed intractable 50 years ago are now being tamed.*" (Niosi & McKelvey, 2018, p. 1099) "*smaller and targeted group of patients (niche markets)"* (Song, 2017, p. 848)
	Customer segments & relationships	Payers: Increased direct relationship Physicians: Sampling and detailing model Patients: Towards disintermediation	"*payers… are increasingly determining market entry, future sales*" (Nuijten, 2014, p. 34) "*Sophisticated and more empowered patients*" (Song, 2017, p. 849)
Value creation	**Key activities**	In-house / Collaborative drug discovery and development activities In-house marketing, regulatory affairs, market access	"*reinforce their marketing*" (March-Chorda et al., 2009, p. 767) "*Outsourcing of value chain activities… New collaboration patterns*" (Song, 2017, p. 848)
	Key partners	Research organizations, Dedicated biotechnologies firms (DBFs), other Big Pharma firms, contract research organizations (CROs)	*"outsourcing R&D tasks to the increasing group of small biopharmaceutical companies*" (March-Chorda et al., 2009, p. 767)
Value Capture	**Revenue streams**	Selling highly priced drugs Conditional reimbursement schemes	"*value-based assessment and risk-sharing agreements, to manage the funding impact of new, premium price, innovative drugs*" (Nuijten, 2014, p. 34)
	Cost structure	Drug development (until marketing authorization) Health economics data	"*most countries require the submission of health economic data*" (Nuijten, 2014, p. 36)

3.2.4.1. IBCO's value propositions

Big Pharma firms have a diversified portfolio of products. According to Gottinger and Umali (2008) Big Pharma products portfolios show an increase in biologic drugs (new molecular entities) rather than new chemical drugs. Two biotechnology-based drugs were among the 10 best-selling drugs in 2010, and six in 2015 (Birkinshaw et al., 2018). Biotechnology-based drugs are often associated with distinct therapeutic value like a new treatment or cure to a previously untreatable diseases, or even their prevention (Hopkins et al., 2007). Biotechnology-based drugs are rather indicated for small segments of the population (Abramawicz, 2011). This shifts the focus of Big Pharma firms toward smaller and better targeted group of patients, defining niche markets (Song, 2017).

3.2.4.2. IBCO's customer segments & relationships

The decision to grant reimbursement is increasingly depending on drug's value for money (Xie, 2018, p. 883). Big Pharma increased their direct relationship with payers to better communicate the value associated with their biotechnology-based drugs. Payers scrutinize the actual value and worth of the new biotechnology-based drugs in terms of improving patient outcomes (Rao, 2010; Xie, 2018) before considering reimbursement status. From the payers´ side, information gaps lead to uncertainty about drug actual value, in terms of *"therapeutic value, cost-effectiveness, optimum application in clinical practice, and budgetary impact"*, which complicates reimbursement decisions (Nuijten 2014, S. 37). Consequently, payers increasingly require formal reimbursement dossier (in most countries) of any novel drug when negotiating its price and reimbursement (Nuijten, 2014). The reimbursement dossiers include budgetary impact and cost-effectiveness data (Nuijten, 2014) and evidence of outcomes or performances (Wenzel et al., 2014) of novel drugs.

No mention in the literature was found to suggest that Big Pharma firms deviated from the sampling and detailing model used with physicians.

"Empowered patients" (Song, 2017, p. 848) are often generating a distinct prescription dynamic than the one from physicians (Rao, 2010, p. 207). Payers increasingly use "*co-payment by the patient*" (Nuijten 2014, S. 40), which raises patients' power over the drug purchase decision. Typically, most healthcare expenses of patients are covered by (third-party) payers.

Patients, who are expecting healthcare services and products to be free or inexpensive have an inkling to spend as littles as possible out of their pockets for drugs (Branning & Vater, 2016). Big Pharma firms provide complementary mobile applications and digital platforms with their biological drugs (Tangour et al., 2019). For instance Abbvie developed an App for patients to follow up their treatments (van der Gronde et al., 2017). Novartis developed an integrated digital environment, the Galaxy of hope to support cancer patients in coping with the psychological symptoms associated with their disease (Tangour et al., 2019). Their use of digital technologies is creating new channels to interact with patients other than through physicians. This form of interaction with patients, does not count as advertising. Direct-to-consumer advertising is illegal in most countries except USA and new Zealand (van der Gronde et al., 2017).

3.2.4.3. IBCO's key activities

In general, *"[f]irms can enter an emerging technological field through internal development or by forming relationships with other organizations*" (Anand et al., 2010, p. 1216). The share of in-house and collaborative activities for biotechnology-based drugs discovery and development vary among Big Pharma firms (Birkinshaw et al., 2018), but few drugs are still totally produced in-house (Boni 2018). In-house R&D activities are relocated within biotechnology clusters to improve R&D outputs, by getting closer to talented researchers and latest technological discoveries (Birkinshaw et al., 2018). For instance, GSK restructured its R&D activities into six autonomous *"'Centers of Excellence for Drug Discovery' to mimic the dynamism of the biotech venture scene"* with units made of 300 to 350 scientists focusing on specific disease areas (Birkinshaw et al., 2018, p. 86). Since 2002, Novartis has been creating a number of Novartis Institutes for BioMedical Research, in global biotechnologies strategic locations for R&D, such as Boston, California, China, India and Singapore (Birkinshaw et al., 2018). In conclusion, for in-house development of biotechnologies based drugs, Big Pharma firms changed their internal organization of R&D activities, by establishing separate units or creating agile structures dedicated to biotechnologies (Birkinshaw et al., 2018).

Big Pharma firms develop the rest through external collaborations. As described in chapter 2, many formats of collaboration exist in theory. In the following the collaboration formats of Big Pharma firms and the key patterns that has been described in the selected literature are presented.

3.2.4.4. IBCO's key partners and collaboration formats

Big Pharma firms count DBFs, contract research organizations (CROs), research organizations and other Big Pharma firms among key partners for the R&D activities related to biotechnologies. Big Pharma firms supply most of their leading-edge biotechnology-based compounds from DBFs (Cockburn, 2004, p. 15). Big Pharma firms invest around 30% of their R&D budget in collaborations with DBFs (Hopkins et al., 2007). Between 1989 and 1999, more than half of R&D investments of 19 Big Pharma firms were through alliances with DBFs (Anand et al., 2010). By 1996, the total number of collaboration with DBFs were the following: "*Eli Lilly, 12; GlaxoSmithKline (GSK), 36; Johnson and Johnson (J&J), 10; Merck & Co, 16; Novartis, 28; Roche, 33; Abbott, 2; AstraZeneca, 5; Bristol-Myers Squibb…, 8; Merck KGaA, 4; Pfizer, 6; and Sanofi, 1"* (Birkinshaw et al., 2018, p. 100). From historical data, it is shown that DBFs are typically small to midsized research-exclusive organization that focus only on few products (Boni, 2012; Downs & Velamuri, 2016; Greiner & Ang, 2012; Sabatier et al., 2010). DBFs are doing well in developing new biotechnology-based drugs in very specialized therapeutic and technological areas (Hopkins et al., 2007). This hyper-specialization renders them very attractive partners to Big Pharma firms (Downs & Velamuri, 2016). DBFs commercialized the outcomes of their research on biotechnologies by leveraging many new BMs (Boni, 2012; Downs & Velamuri, 2016; Greiner & Ang, 2012; Sabatier et al., 2010), where they delivered either an R&D-intensive value proposition or simply supplied biotechnology-based services and technologies (Greiner & Ang, 2012; Sabatier et al., 2010). For instance, the so-called the Fully Integrated Development Organization (FIDO) BM of certain DBFs, consisted in the delivery of new biotechnologies-based drug candidates to Big Pharma firm in exchange of some form of payment (e.g. Royalty fees) (Boni, 2019). Big Pharma firms took these acquired drug candidates through the following steps of a drug's lifecycle (i.e. clinical trials, regulators affairs, distribution and marketing) (Boni, 2019). Drug's development can be outsourced using fee-for-service agreements to specialized companies called contract research organizations (CROs) (Nicol et al., 2013). CROs are being used since the 1980s to outsource human clinical trials, and is even becoming a standard in the industry (Nicol et al., 2013).

Big Pharma firms partnered with research organizations to gain access to technology via knowledge spillovers and talented people (Downs & Velamuri, 2016).

According to Birkinshaw et al. (2018, p. 84) *"Partnering with… universities involved in an emerging technology is a means of building expertise and knowledge of who the key players are in an emerging space".* Firms engage with research organizations Nevertheless, literature emphasizes the importance of inter-firms collaborations over the one with research organizations since academic research is becoming less vital to gain access to biotechnologies (Downs & Velamuri, 2016).

Big Pharma firms merge with other Big Pharma firms or, more rarely, acquire other Big Pharma firms. No other forms of collaborations have been found in the literature. In the following, different collaboration formats with each key partner are detailed.

Big Pharma firms diverge from their dominant in-house R&D activities (Nicol et al., 2013; van der Gronde et al., 2017) to develop new collaboration patterns (Song, 2017). As presented in Chapter 2, the different collaborations a company can form with other organizations can be devised into equity-based and non-equity-based collaborations. A matrix is made with all the theoretical collaboration formats and key partners. The selected literature is searched for each combination of collaboration format and partners and possible examples (e.g., Licensing & DBF). Table 6 provides an overview of this systematic analysis of the literature for key collaboration formats designed in the IBCO.

Table 6. Key collaboration formats of Big Pharma firms described in the IBCO for gaining access to biotechnologies with examples (Source: Own table)

Collaboration formats	**DBFs**	**Research organizations**	**Other Big Pharma firms**
Licensing arrangements	Pfizer / BioNTech (2018; mRNA technology platform)	AstraZeneca / Oxford University (2020)	Not Found
Other collaborations	Pfizer / BioNTech (2020; COVID vaccine)	Bayer/German Cancer Research Centre (2008)	Not Found
Corporate venturing	Merck Capital Ventures (Merck & Co., 2000)	Not Found	Not Found
Mergers	Not Found	Not Found	Astra & Zeneca = AstraZeneca (1999)
Acquisitions	GenenTech ∈ Roche (1990)	Not Found	Wyeth Pharmaceuticals ∈ Pfizer (2000)

a. Licensing agreements and other non-equity-based collaborations

The licensing could concern a drug candidate or technology platform. In the case of biotechnologies, platforms refer *"to common foundation (or, technological) base from which one can create a family of products (and services), while targeting different customer segments. e.g. multiple disease states" (Boni, 2019, p. 9).*

Big Pharma firms pursue most new biotechnology projects with DBFs via licensing arrangements (Boni, 2012, 2019; Greiner & Ang, 2012). For instance in 1993, Human Genome Sciences sold to GSK genetic sequence data, used to identify new drug targets (Hopkins et al., 2007). More recently, in 2018, a licensing agreement was made by and between Pfizer and BioNTech (DBF) concerning the rights of the biotechnology fields of modified Ribonucleic acid (RNA) technology or replicon technology (SEC, 2018). As part of this agreement, BioNTech grants an exclusive license to Pfizer for the usage, development, manufacturing and exploitation of candidates and products in a specific geographic territory (SEC, 2018). This license does not completely prevent BioNTech and its affiliates from conducting further internal research (SEC, 2018). A good example of licensing agreements between Big Pharma firms and research organization is the one between AstraZeneca and Oxford University (AstraZeneca, 2020). The ChAdOx1 nCoV-19 vaccine is developed by the Jenner Institute and Oxford Vaccine Group at the University of Oxford and is globally commercialized under the AstraZeneca brand name (AstraZeneca, 2020). Other non-equity-based collaborations such as joint R&D contracts, supplier co-makership contracts and R&D contracts are delimited to specific projects (Birkinshaw et al., 2018) such as technology exchanges, testing agreements and research contracts (Anand et al., 2010) between two or more organizations. For instance, in 2020, Pfizer Inc. and BioNTech SE defined a collaboration agreement to develop and commercialize candidates for a vaccine against the COVID-19 vaccine (SEC, 2020). In this collaboration Pfizer has rights of commercialization in countries except those where BioNTech has the right to exclusively commercializing such as Germany and Turkey. The strategic partnership signed in 2008, between Bayer HealthCare Pharmaceuticals and the German Cancer Research Centre (DKFZ) is a join R&D contracts for the development of new oncological drugs (Pwc, 2009). Four Big Pharma companies (Bristol-Myers Squibb, MSD, Pfizer and Roche) jointly financed the research of a consortium of Germany research organizations on the health economics benefits of using a combination of therapies in oncology (Gothe et al., 2021).

b. Equity based collaborations: Corporate venturing, mergers, and acquisitions

Certain firms like Johnson & Johnson used existing venture capital funds (J&J Development Corporation) to make early success in biotechnologies. Others, decided to create investment funds *de novo* to invest selectively in biotech alliances such as Merck Capital Ventures by Merck & Co.

Mergers of giant impregnated the early 21st century period. SmithKline Beecham and GlaxoWellcome merged to form GSK in 2000 and Astra and Zeneca merged in 1999 to form AstraZeneca (Birkinshaw et al., 2018; Demirbag et al., 2007). SmithKline made early investments in vaccine development bioinformatics, and genomics and GlaxoWellcome bought a biotechnology firm called Affymax (Birkinshaw et al., 2018). Warner-Lambert and Pfizer merger in 2000 under the name of Pfizer only, which is described as a hostile deal (Demirbag et al., 2007). Literature don't mention any mergers of companies from different sized such as Big Pharma firms and small DBFs.

Big Pharma firms mostly acquired small and medium-sized DBFs with their whole product portfolios (Birkinshaw et al., 2018; Boni, 2018; Downs & Velamuri, 2016; Gottinger & Umali, 2008; March-Chorda et al., 2009). Parts or the whole of the acquired company continued its operations as part of the Big Pharma acquiring firm (Boni, 2012). One of the first acquisitions was of Hybritech (specialized in monoclonal antibody) in 1986 by Eli Lilly for US$350 million. Between 1990 and 2013, all of AstraZeneca, Abbott, Bristol Myers Squibb, Eli Lilly, Johnson & Johnson, Merck & Co., Merck KGaA, Pfizer, Sanofi, GSK, Novartis, and Roche acquired DBFs and firms with biotechnologies activities (Birkinshaw et al., 2018). Merck & Co. acquired many established DBFs with blockbuster drugs with remaining patent life (Tulum & Lazonick, 2018). In 2009, when Pfizer's patent for its blockbuster Lipitor was nearing expiry, it acquired Wyeth Pharmaceuticals, another Big Pharma firm, for $68 billion (Song & Han, 2016). Roche acquired a controlling stake of Genentech in 1990 for US$2.1 billion, after Merck and many other Big Pharma firms declined this opportunity (Birkinshaw et al., 2018).

Big Pharma firms increasingly reinforce the vertical integration of their marketing and market access activities (March-Chorda et al., 2009). Rather than outsourcing pricing and reimbursement activities, Big Pharma firms decided to establish their own health economic departments (Nuijten, 2014, p. 36). This denotes a shift in the key activities for drugs R&D, to regulatory and market access activities. Nuijten (2014) confirms that the market access activities (pricing and reimbursement) have become a key part of the drug development process.

3.2.4.5. IBCO's revenue streams and cost structure

At the beginning of the millennium, a new drug costed on average between $900 million and $1.3 billion (2005 dollars) until it was a granted a marketing authorization (Downs & Velamuri, 2016; Horvath et al., 2019). Today's drug development could be rather accelerated but not made cheaper, since R&D activities are targeting more complex diseases which generates more costs (Cockburn, 2004, p. 12). For instance the costs for establishing genomics capabilities is between $100 and $300 million (Gassmann et al., 2018). Additionally, requirements for cost-effectiveness, budgetary impact and other related data are increasing expenditures for Big Pharma firms (Nuijten, 2014). These data are often generated via additional clinical trials and new health economic departments, in charge of all drug pricing and reimbursement activities are often established (Nuijten, 2014).

The increasing cost associated with healthcare are leading payer to exert more pressure on Big Pharma firms to reduce their profit margins (Downs & Velamuri, 2016, p. 20). New risk-sharing schemes, also called conditional coverage agreements or conditional reimbursement approaches have been emerging as new models to ensure payment for novel drugs by payers while limiting heath costs (Nuijten 2014, S. 34). There are financial-bases models and outcomes-based models for the negotiation of conditional reimbursement of drugs (Nuijten, 2014). In the financial-based models, payers may agree on price-volume agreements (PVAs), price dependent on market share achieved or patient access schemes (PASs). The outcome or performance-based models can be in at least three forms, the temporary reimbursement, limited reimbursement within prescription restrictions and pay-for-performance (Nuijten, 2014).

Pricing the new drugs higher is another strategy (van der Gronde et al., 2017). Since revenues are calculated by multiplying the price by the volume, Big Pharma firms adopted a strategy of price increase to cope with decreased volume of sales due to the smaller population size of many new biotech drugs and the reduced number of new blockbuster introduced, to generate adequate revenues (van der Gronde et al., 2017, p. 12). Higher drug prices protect Big Pharma's high-profit revenue profile (van der Gronde et al., 2017). The price definition relates to cost-effectiveness only if the payer introduces this requirement in the negations (van der Gronde et al., 2017, p. 9). The price is defined based on the price of the standard treatment plus a premium, depending on the payer's willingness to pay or the uncertainty of the value of the new drug (van der Gronde et al., 2017). A drug's price is rather related to the potential to maximize revenues rather than the drug's development costs (van der Gronde et al., 2017). Since Big Pharma firms are for-profit entities, they aim at profits maximization and increase of shareholders value (van der Gronde et al., 2017). Big Pharma have an average profit margins of 16% to 20% that are considered relatively higher than the average 7% of companies from other sectors (van der Gronde et al., 2017).

In conclusion, the literature mentions many elements of Big Pharma firms' BMs. They are grouped in two main BM designs: FIPCO (before 1980s) and IBCO (after 1980s). Secondly, various collaboration formats for R&D between Big Pharma firms and dedicated biotechnology firms, research organizations and other Big Pharma firms are found to be IBCO's key activities (e.g., mergers, acquisitions, corporate venturing, and licensing). Non-equity-based collaborations between competing Big Pharma firms (e.g., licensing) are not mentioned in the literature searched. Thus, further research is needed to verify the accuracy of these results to the reality of the practice. Additionally, some aspects that are relevant to the practice could be missing in scientific discourses. An empirical study allows to reach possible explanations for the missing data, either in the design of the BMs or the types of collaborations. Furthermore, the empirical research should also be designed to provide possible deviant cases or examples to refine the initial hypothetical statements underpinning the BM designs of the FIPCO and the IBO.

4. Validated Big Pharma Firms' Business Models and Their Collaboration formats

The first goal of this chapter is to verify the accuracy of the two BM designs derived from the scientific literature. The second goal is to systematically explore various collaboration formats of Big Pharma companies, and their benefits and risks. For both purposes a qualitative content analysis of semi-structured interviews with experts in the pharmaceutical industry is conducted. Beyond confirming what was found conceptually, expert interviews can uncover new insights on BMs of Big Pharma firms. The chapter starts with a presentation of the methodology followed by the results.

4.1. Methodology: Qualitative expert interviews

The study's research interests are limited to the following research sub-questions:

- What is a design of the FIPCO BM that is accurate to the practice's reality?
- What is a design of the IBCO BM that is accurate to the practice's reality?
- In which kind of collaboration do Big Pharma firms engage, with reference to biotechnology-based drugs? How can these collaborations be characterized?

In the following, methods used for data collection, analysis and validation are described in detail.

4.1.1. Data types and data collection strategy

Qualitative data are non-numerical, unstructured data (Rädiker & Kuckartz, 2018), in text or audio-visual formats (e.g. newspapers or photographs) (Bryman & Bell, 2015; Creswell, 2009). Qualitative data can be empirical or secondary. Empirical qualitative data are created during a research project while secondary data are antecedent to it (Bryman & Bell, 2015). In this work, it was chosen to collect secondary data to support empirical findings with examples from the practice. Secondary data consists in internet documents found in U.S. Securities and Exchange Commission reports, companies' press releases, and newspaper articles.

4.1.1.1. Empirical qualitative data collection method

Methods of empirical qualitative data count participant observations, interviews or a mixture of both approaches (Bryman & Bell, 2015).

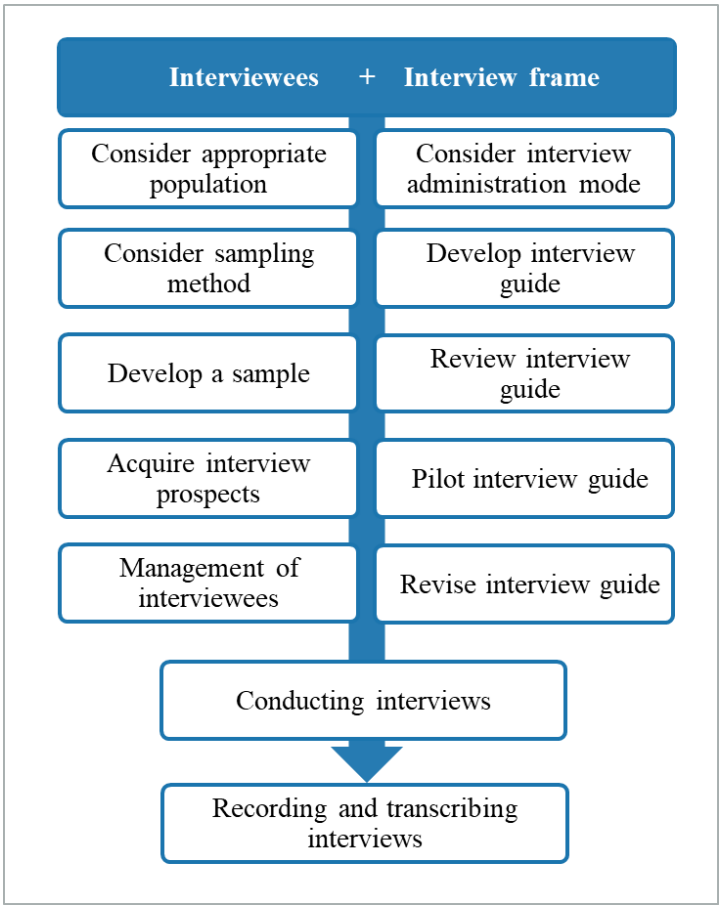
The method of participant observations is not fitting to collect data for this study, for at least two reasons. This method is recommended for a different research focus, one that focus on a specific social setting, such as an organization or social group (Bryman & Bell, 2015). Furthermore, this method does not necessarily imply the active extraction of responses from participants (Bryman & Bell, 2015).

Consequently, in this study interviews are conducted. *Interviewing* is a technique, in which an interviewer aims to elicit from the interviewee all manner of information (Bryman & Bell, 2015). Research interviews are the most prominent and widely employed method for data collection in business research (Bryman & Bell, 2015; Creswell, 2009). Interviews can be conducted with one interviewee at a time (i.e. induvial interviews), or with two or more interviewees (i.e. focus groups) (Bryman & Bell, 2015). In this study individual interviews are preferred to focus groups, since group interactions are not critical aspects of this research. Individual qualitative interviews can be unstructured or semi-structured (Bryman & Bell, 2015). Semi-structured interviews are chosen because of two reasons. First, they allow more reproducibility between interviews, since they admit a higher degree of standardization than unstructured interviews (Bryman & Bell, 2015). Second, they allow enough flexibility to leave room uncover adjacent topics to the research question (Bryman & Bell, 2015).

4.1.1.2. Steps of the semi-structured interviews

The process of conducting semi-structured interviews is described in Figure 14. This process is adapted to this research and described in the following five steps from (a) to (e).

Figure 14. Process of conducting semi-structured interviews (Source: Own figure based on Bryman & Bell, 2015)



a) Targeting interviewees' population

Interviewees must have knowledge of BM designs of Big Pharma firms. They are in *"the position of informants rather than as respondents answering questions about themselves" (Bryman & Bell, 2015, p. 253).* They provide expert opinions on "*characteristics of an entity of which they have knowledge" (Bryman & Bell, 2015, p. 253).* Interviewees are to be found among top or middle managers in Big Pharma companies, business consultants and business researchers, who focus their professional activities on the way Big Pharma firms manage their businesses. Experience in biotechnology applications in the pharmaceutical industry is required.

b) Interviewees' sampling method

A purposive sampling approach is adopted, since representative sampling is rarely feasible in qualitative research due to conditions in field work, or difficulties in mapping the general population (Bryman & Bell, 2015). Most purposive sampling approaches used by qualitative researchers rang from convenience (or opportunistic) sampling method, to theoretical sampling (Bryman & Bell, 2015).

In this research, the following selection criteria serve to purposefully select a sample of potential interviewees: (1) geographical reach, (2) experience in pharmaceutical industry, (3) experience with biotechnologies and (4) interaction with various stakeholders. All interviewees (except consultants and researchers) should be in mid or top management positions, preferably currently working in a Big Pharma firm, and/or with previous working experiences in Big Pharma firms. They are selected considering different geographical reaches, from a national, to a regional and to a global reach. Since this research does not compare managers' specific opinions, a focus on a certain level of expertise is irrelevant. Junior managers (less than five years in position), who only knew the pharmaceutical industry after the advent of biotechnologies and the internet, could have a different interpretation of the reality of practice than more experienced managers. Selected managers are in positions requiring interactions with a wide spectrum of stakeholders (e.g., country managers, or global marketing managers).

Bryman and Bell (2015, p. 429) advise to make use of all available resources and personal contacts within ethical guidelines to gain access to interviewees. Managers and consultants are identified based on personal contacts or referrals, or through a search on the business network LinkedIn. Researchers in the pharmaceutical industry are selected based on their published work.

c) Developing interview guide

The interview guide consists of specific questions, that create order and flow among interview topics (Bryman & Bell, 2015). According to Kvale (1994), in a good interview guide different categories of questions, such as presented in Table 7, are used. Interviews are conducted in English or French, at interviewees' convenience.

Table 7. Different kinds of question that can be asked in an interview guide (Source: Own table)

Kinds of questions (Kvale, 1994)	**Types of question (Bryman & Bell, 2015)**
Introducing questions	Personal factual questions
Follow-up questions	Factual questions about others
Probing questions	Informant factual questions
Specifying questions	Questions about beliefs
Direct questions	Questions about attitudes
Indirect questions	Questions about normative standards
Structuring questions	Questions about knowledge
Interpreting questions	

The English version of the interview guide used for this study can be found in Appendix 3. It consists of informant factual questions and questions about beliefs of interviewees as well as personal, follow-up, and specifying questions. Following the recommendations of Bryman and Bell (2015), the interview guide is a mix of closed and open questions that are formulated in a simple language free from unnecessary jargon. Open questions ensure that *"interviews will allow novel or unexpected themes and issues to arise"* (Bryman & Bell, 2015, p. 498). In general, leading questions are avoided. In certain circumstances, structuring or interpreting questions are used to ensure that interviewees' statements are correctly understood.

Each interview in this research is divided in three parts. Question in part 1 concern the accuracy to practice of conceptually derived FIPCO and IBCO. In part 2, questions focus on collaboration formats employed by Big Pharma firms and their benefits, advantages, and risks. In part 3, personal questions are asked to agglomerate and analyze data.

Along site the interview guide, visual aids presenting the conceptually derived FIPCO and IBCO, collaboration formats of Big Pharm firms and six show cards are used (see Appendix 3). Visual aids are visual artifacts used as reference points for discussions (Bryman & Bell, 2015). Interviewees can be asked to comment, explain, and describe associated thoughts elicited by the visual aid (Bryman & Bell, 2015). For instance, show cards visually display all answers of closed questions, from which interviewees read and chose their answers (Bryman & Bell, 2015). In general, the use of show cards is better for the interview flow than reading a very long list of fixed-choice answers (Bryman & Bell, 2015).

d) Acquiring, managing, and administering interviewees

Prospect interviewees are contacted via emails (when publicly available), or via direct messages in LinkedIn. LinkedIn profiles of interviewees are saved and used to evaluate the correspondence of a potential expert to selection criteria. An excel sheet is developed to manage contacts, reminders and to document all the steps in acquiring interviews. Interviewees' identity is pseudonymized, with "IP n", in which IP stands for Interview Partner and n is interviewees attributed number. Face-to-face interview administration mode is not possible because of global locations of interviewees. Other alternatives are telephone or video call interviews.

Telephone interviews do not allow for the observation of interviewee's reactions, and exclude the use of visual aids (e.g. show cards or figures) (Bryman & Bell, 2015). Due to the high level of complexity of the conceptually derived BMs (FIPCO and IBCO) the use of visual aids is a great support for conversations with interviewees. By selecting video call as the administration mode of interviews, observation of interviewee's reactions and the use of visual aids are made possible.

e) Conducting, recording, and transcribing interviews

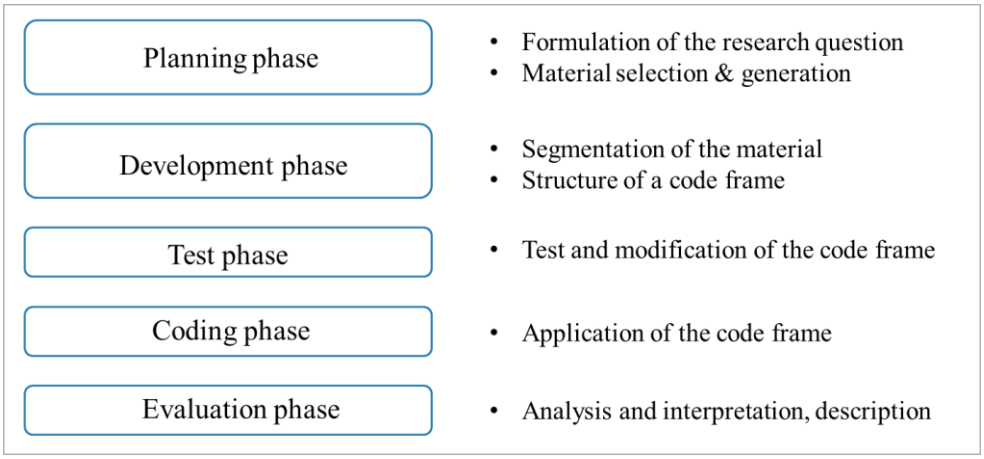
Interviews are conducted using the video call software Microsoft Teams. The interviewer's screen is shared with interviewees to display the visual aids. The software OBS Studio serves to record the audio of the interviews. The Audacity software serves to convert all audio files from MP4 to MP3 formats. At this stage interviews that happened in two different appointments are merged into one audio file. The recorded interviews are then transcribed by a third-party service firm. Any personal information that could lead to the identification of an interviewee's person have been anonymized or removed from final transcripts.

4.1.2. Data analysis

Qualitative methods of data analysis range from hermeneutics at one end, to content analysis at the other end of the spectrum. They aim to interpret, approximates, characterizes, and categorize qualitative data (Bryman & Bell, 2015; Kuckartz, 2019; Mayring, 2019). Hermeneutics emphasizes the perspective of social actors in interpreting meaning of human actions (Bryman & Bell, 2015). From a methodological point of view, very little orientation or rigor is provided by hermeneutics (Kuckartz, 2019; Mayring, 2019). At the other end, content analysis provides a rigorous framework *"to the analysis of documents and texts… that seeks to quantify content in terms of predetermined categories and in a systematic and replicable manner"* (Bryman & Bell, 2015, p. 289). Qualitative content analysis is between the depth of understanding of hermeneutic analysis and the systematic process of the classic content analysis. Qualitative content analysis *"is a method for systematically describing the meaning of qualitative data"* (Schreier, 2014, p. 170). This method is frequently used by German speaking researchers as two of its leading authors published their seminal work in German (Kuckartz, 2016, 2019; Mayring, 2015, 2016, 2019).

In Kuckartz (2014) three basic methods of qualitative text analysis are explained, while Mayring (2015) describes eight variations of the method (e.g. evaluative, scaling, type-building and explicative). The different methods of the qualitative content analysis are not actual variations of the whole process but are parts of it (Stamann et al., 2016). Figure 15 presents the general steps that are frequently used for conducting qualitative content analysis.

Figure 15. General steps for a qualitative content analysis (Source: Own figure based on Kuckartz, 2014; Mayring, 2015; Schreier, 2014)



4.1.2.1. Coding texts using MAXQDA

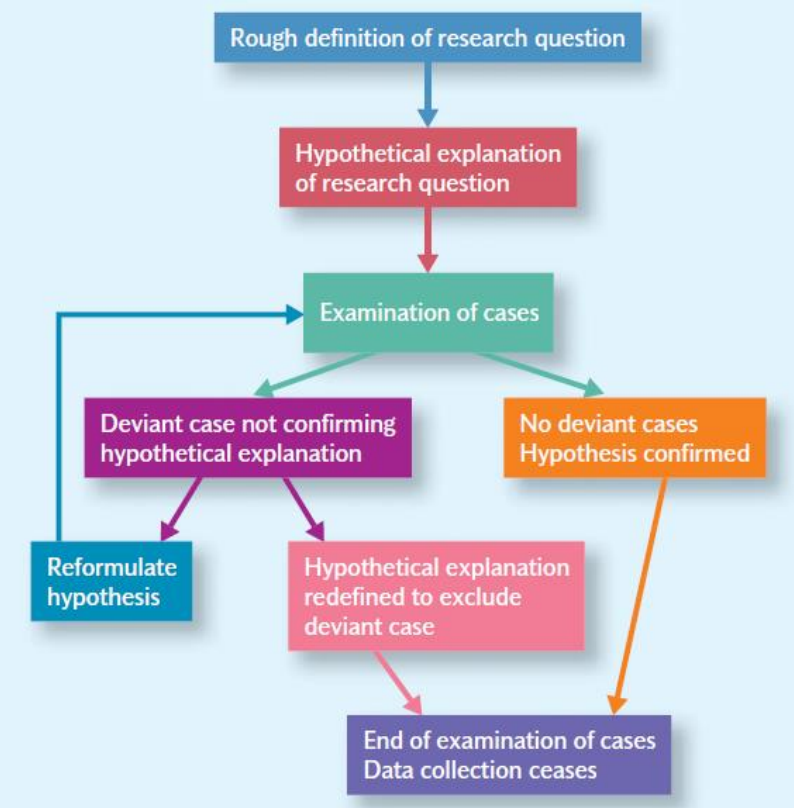
There are at least three commonly used computer assisted qualitative data analysis software (QDAS), designed to facilitate the management and analysis of qualitative data: ATLAS.ti (Silver & Lewins, 2014), NVivo (Richards & Richards, 1994) and MAXQDA (Rädiker & Kuckartz, 2018). For this research, MAXQDA is preferred to the other QDAS for it allows transcripts to be synchronized with audio files and to be played back (Rädiker & Kuckartz, 2018). In MAXQDA, researchers assign codes (categories) to selected parts of the data, organize them in sub-categories and can add memos and comments (Rädiker & Kuckartz, 2018). The coding frame is developed in three phases. First, before starting to code transcripts, a first coding frame is derived deductively, based on questions from the interview guide. Second, a sample of five randomly chosen transcripts are coded with the first coding frame. This way, the first coding frame is tested and improved by creating new codes *in-vivo*. This means that new categories are inductively added to the coding frame. Finally, all transcripts, including the sample used during the testing phase, are coded according to the final coding frame. Coded segments are evaluated following the method of analytic induction.

4.1.2.2. Analytic induction

The method of analytic induction is used for the analysis, interpretation, and description of data. Analytic induction is an iterative process (see Figure 16) that allows researchers to qualitatively test hypotheses, in order to sharpen and better delimit them (Bryman & Bell, 2015). This method is followed to qualitatively devise a validated version of the conceptually derived BMs in chapter 3. Each cell of the conceptually derived BMs is considered a separate hypothesis. Interviewees either support the BM statements or generate new statements to correct or complete the BM designs.

During this phase, internet documents are searched and analyzed, in addition to interview, to complement examples provided by interviewees. Through interviews and publicly available documents, initial designs for the FIPCO and IBCO are empirically adjusted and validated. In conclusion, analytical induction provides researchers with the flexibility to, not only confirm or refute what has been conceptually derived, but also to infuse new insights. New elements emerge through the interview study and constitute a contribution to the literature in the realm of BM of Big Pharma firms.

Figure 16. Process of analytic induction (Source: Bryman & Bell, 2015)



4.1.3. Quality criteria for qualitative empirical studies

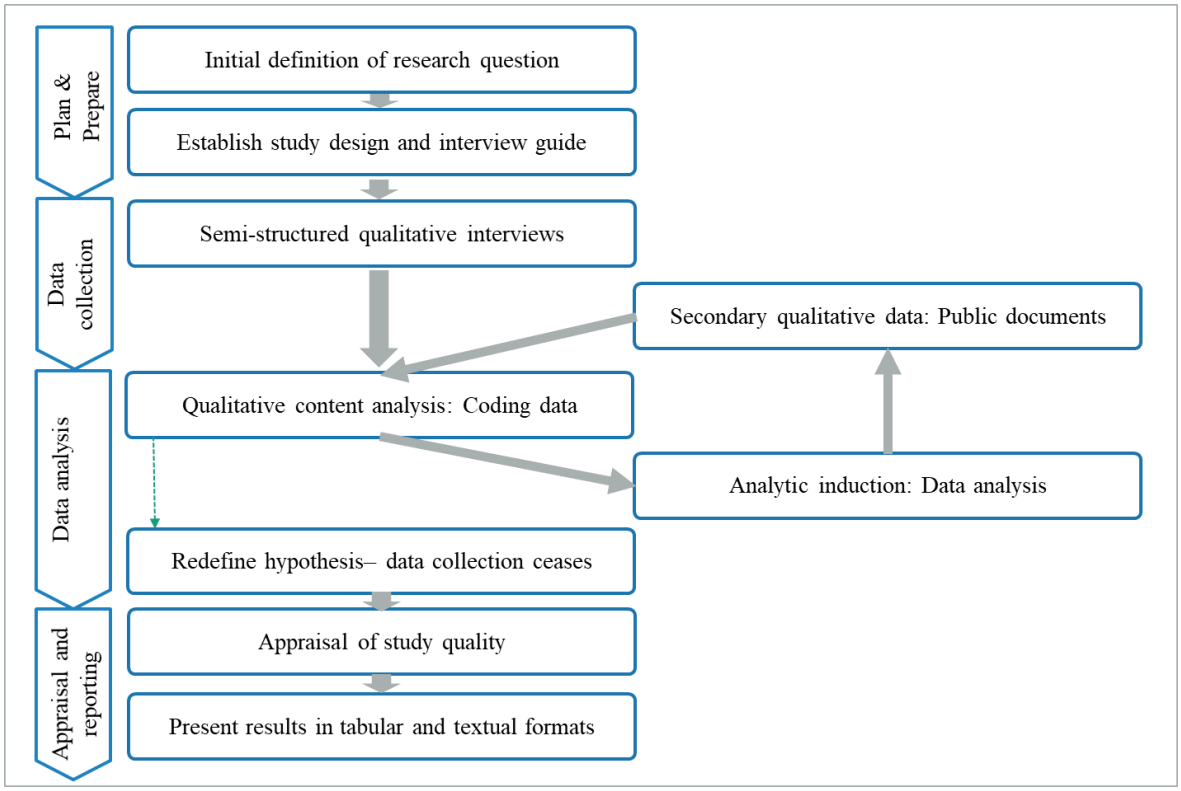
Many qualitative researchers choose to use an adapted definition of reliability and validity concepts for qualitative research (Bryman & Bell, 2015). They slightly change the meaning of the concepts and minimize the importance of measurement (Bryman & Bell, 2015). Other qualitative researchers develop alternative quality criteria for evaluating qualitative research (Bryman & Bell, 2015). Guba and Lincoln (1994) propose trustworthiness and authenticity as two new main criteria to establish and asses the quality of qualitative research. Mayring (2016), a leading scholar in the method of qualitative content analysis, establishes six quality criteria (see Table 8). Criteria for the appraisal of the study as defined by Mayring (2016) are applied to ensure and demonstrate the validity, objectivity and reliability of this empirical study (i.e. process documentation, argumentative safeguarding of interpretation, rule guidance, proximity to the subject, communicative validation and triangulation).

*Table 8. Qu*ality criteria for evaluation qualitative research methods (Source: Own table based on *Mayring, 2016*)

Criteria	**Definition / Characteristics**
Procedural documentation	- Detailed documentation to make the research process comprehensible - This includes the explication of the prior understanding, compilation of the analytical instrument, implementation, and evaluation of the data collection
Argumentative safeguarding of interpretation	- Interpretation must be justified argumentatively - Prior understanding of the interpretation must be adequate and conclusive - Justification of negative cases
Rule guidance	- Step-by-step and sequential approach to data collection and data analysis - The analysis process is broken down into individual steps, which are systematized
Proximity to the object	- The object of investigation is as close as possible to the everyday world
Communicative validation	- Validity of the results can be checked by submitting or discussing the results to the researched again for validation
Triangulation	- The quality of the research can be increased through several analysis steps - Different data sources can be used (e.g., interviews, documents, website), different researchers & interpreters, application of multiple theories and hypotheses

Figure 17 represent a summary of the semi-structured interviews conducted in this study. As shown in this figure, this empirical study respects the above-mentioned quality criteria. The quality criteria of process documentation, the argumentative safeguarding of interpretation, the rule guidance, the proximity to the object and triangulation are present in this study. For instance, research focus and explanation behind the choice research design are provided. Moreover, internet documents are added to diversify data sources. Only the communicative validation is not completely available since the results are not discussed again with the interviewees. However, they are discussed with other researchers operating in the field of BM innovation.

Figure 17. Process of the qualitative empirical research design (Source: Own figure)



4.2. Results: Validated business models of Big Pharma firms

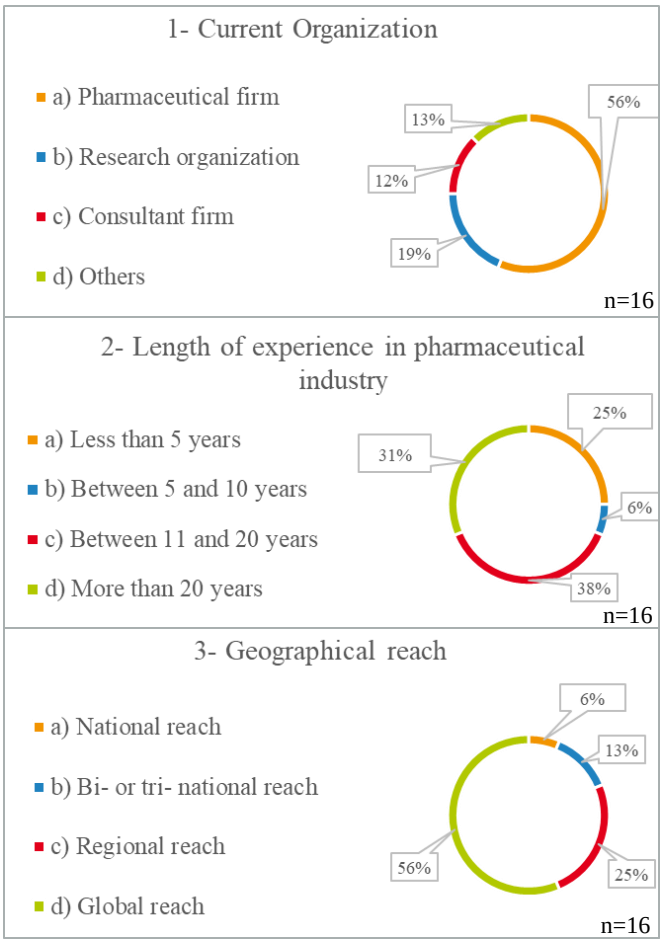
The focus of this thesis is on how Big Pharma firms accommodated biotechnologies in the design of their BM. In this chapter, the two conceptually derived BM designs (see Tables 4 and 5) are qualitatively validated. Furthermore, collaborations in which Big Pharma firms engage to create value around biotechnologies are further explored. The basis for this exploration is Table 6 (chapter 3), in which the presence of theoretically possible formats of collaboration in the Big Pharma's current BM is documented based on the literature. Experts are asked about the existence of theoretically possible collaboration formats that are not described in the literature (see Table 6). Furthermore, the advantages and risks of external collaborations is studied. This section starts with a description of experts' characteristics. The results of the interviews are presented in the form of two validated BM designs (IBCO and FIPCO) and the documentation of all collaboration formats of Big Pharma firms.

4.2.1. Description of interviewees

During the interviewees' acquisition process, 32 potential experts in the pharmaceutical industry are selected and contacted (see 4.1.1.3). From this contact list, 19 initially accepted to participate in the interview study, nine experts did not reply, and four declined to participate. Interviews are conducted from March 27th until April 16th, 2021, during which three potential interviewees additionally declined to participate due to time constrains. The final sample of interviewees consist of 16 experts in the pharmaceutical industry.

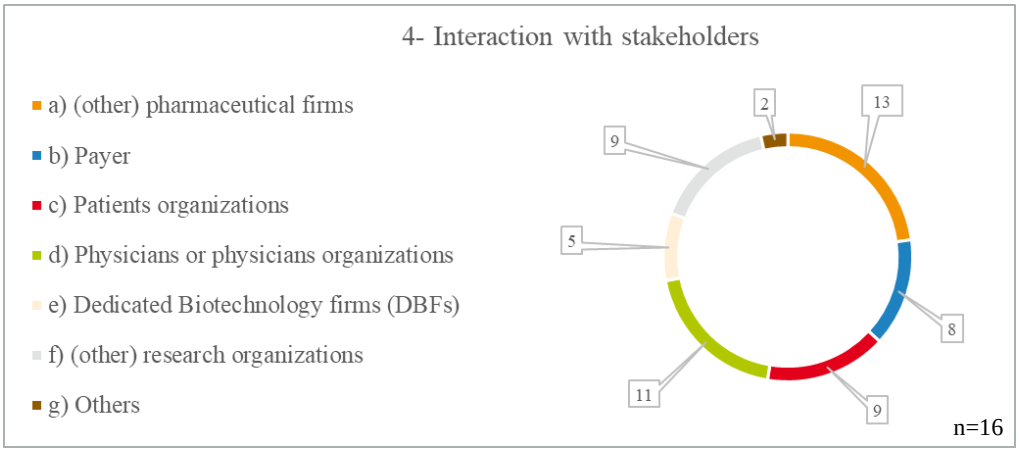
In this study, interviewees are purposefully sampled to ensure a level of variety among the selection criteria: (1) Geographical reach, (2) Experience in pharmaceutical industry, (3) Experience with biotechnologies and (4) Interactions with various stakeholders. As Figure 18 shows, more than half of the interviewees are currently working in a pharmaceutical firm (n=9). Currently, seven of those are in middle or top management positions in Big Pharma firms. The remaining two are a top manager in a DBF and a senior manager in a local pharmaceutical manufacturer who count in their career manager positions in Big Pharma firms. Furthermore, 69% of interviewees have more than 10 years of experience in the pharmaceutical industry. More than half of the interviewees had activities with a global reach. Interviewees are located in Belgium, Germany, India, Japan, New Zealand, Switzerland, Tunisia, United Arab Emirates and USA.

Figure 18. Experience of interviewees in the pharmaceutical industry and their geographical reach (Source: Own figure)



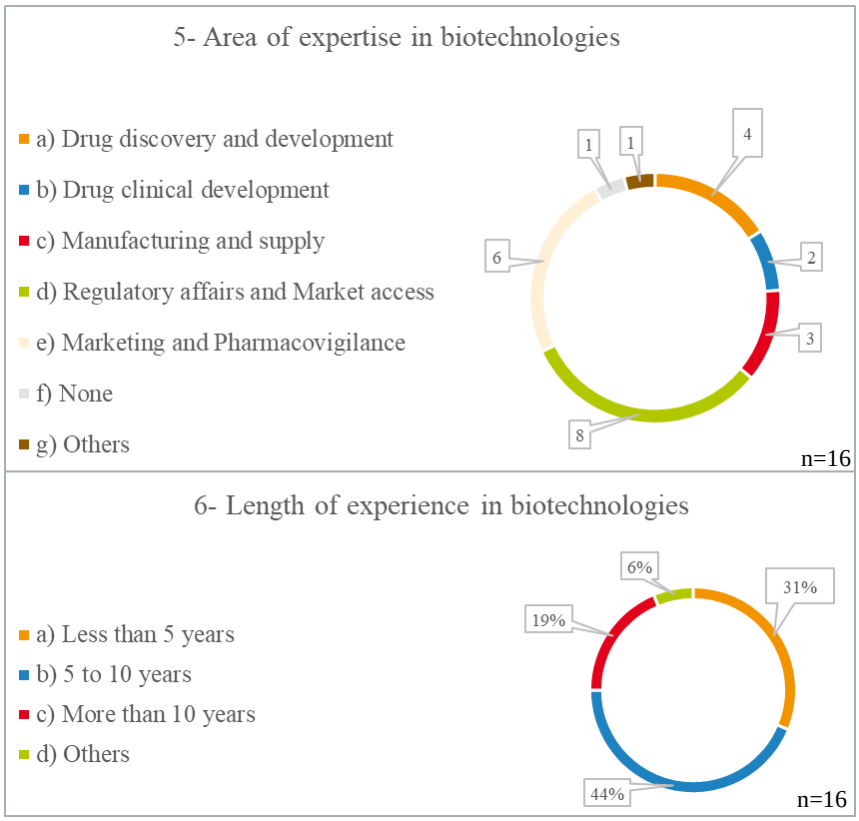
As shown in Figure 19, the 16 interviewees have professional interactions with stakeholders of the pharmaceutical industry. They include customer segments (i.e., payers, patients, and physicians), key partners (i.e. DBFs, research organizations and other pharmaceutical companies) and two others (i.e. contract manufacturing organizations and healthcare authorities).

Figure 19. Interactions of interviewees with various stakeholders in the pharmaceutical industry (Source: Own figure)



Finally, it is essential for interviewees to have working experience with biotechnologies. Except for one interviewee, all possess diversified areas of expertise in biotechnologies-based drug's value chain (see Figure 20). This one interviewee is not directly responsible for biotechnology-based drugs. Nevertheless, as a top manager in a Big Pharma firm, they are involved in strategic decisions concerning biotechnologies-based drugs. Finally, only 19% of them have more than 10 years of experience in working with biotechnologies.

Figure 20. Experience of interviewees with biotechnologies (Source: Own figure)



In conclusion, the selected interviewees fit the selection criteria defined in 4.1.1.3. In total 1085 minutes of interviews are recoded and transcribed. An average interview lasts 68 min. On average 58 text segments are coded per interview. In total 935 text segments are coded using the code system described in Appendix 4. In the following, the validated FIPCO and IBCO, after integration of all experts' insights, are presented.

4.2.2. Validation of the FIPCO based on expert interviews

More than half of the interviewees (10) judged that the FIPCO is completely accurate, while the rest (6) found it accurate to some high extent. Results from interviews and publicly available documents are summarized in the validated FIPCO of the Big Pharma firms (see Table 9). In the following, the differences to the FIPCO design derived from scientific literature (see Table 4) are marked. All segments marked in grey are BM elements that emerged through the current study and are a contribution to the literature on BM of Big Pharma firms. Most noticeable new contributions are:

- The FIPCO design includes the commercialization of biologic drugs by Big Pharma firms. However, at that time, these type drugs emanate from biologic extraction and not from biotechnologies.
- Big Pharma firms have collaborations with other Big Pharma firms and dedicated chemicals firms before the advent of biotechnologies.

Table 9.Before the 1980s: the validated Fully Integrated Pharmaceutical Company (FIPCO) business model (Source: Own table)

Business model dimensions		**FIPCO**
Value Delivery	**Value propositions**	Drugs from chemical synthesis frequently in pills Biologic drugs from biologic extraction Auto-generics (occasionally after patent expiration) One-size-fits-all value of drugs targeting mass markets
	Customer segments & relationships	Payers: Formal and superficial relationships Physicians: B2B via sales force with poorly scientific arguments, and sampling model Patients: direct advertisement
Value Creation	**Key activities**	In-house drug discovery and development + limited collaborations In-house marketing, regulatory affairs, manufacturing (with limited outsourcing)
	Key partners	Other Big Pharma firms Dedicated chemicals firms
Value Capture	**Revenue streams**	Selling drugs
	Cost structure	Drug discovery and development Operational costs

Segments marked in grey highlight differences resulting from the interviews to Table 4.

4.2.2.1. FIPCO'S validated value propositions

The value proposition in the FIPCO is relying on chemical drugs. Three interviewees noticed some missing parts to the overall value proposition offered by Big Pharma firms before the 1980s. First, Big Pharma firms offered their own generic drugs. *"[Companies are used to making auto-generic sometimes when the product falls into the public domain]"* (Translated from French IP-2: 135). For instance, since 2005, Sanofi has a generics division run under the name Winthrop (Sanofi US, 2021). They produce and sell no less than 10 auto-generic drugs, such as Alfuzosin Winthrop® (Sanofi US, 2021). In 2008, Zentiva was included to the Sanofi Generics Franchise and become Sanofi's generics platform in Europe (Zentiva, 2021). Second, Big Pharma did commercialize biologic drugs before the advent of biotechnologies. IP-17 pointing out that biologic drugs were already produced long before the advent of biotechnologies (IP-17*)*. The hypothesis that Big Pharma firms only offered chemical drugs was not correct in the FIPCO's BM design (see Table 4).

IP-17 mentions the example of the Insulin Novo® commercialized as of 1925 by Novo Nordisk (founded in 1923). [*At that time ... they were working with the living world that is to say… with insulins or proteins. You see it already existed. So maybe 80% of the model was chemical. I think there were already biotechs - that were there*] (Translated from French IP-17: 12). In this example the biologic drug was produced through a process of extraction from animal pancreas (e.g., pigs) and not synthetized by using biotechnologies. As shown in Table 9, biologic drugs from biologic extraction are offered by Big Pharma firms but not biotechnology-based drugs.

Admittedly, interviewees agree that Big Pharma firms offered predominantly one-size-fits-all value of drugs, the "*it was primarily focused on mass markets"* (IP-8: 47). Big Pharma firms wanted to cover "*the majority of good -, you know, main diseases, chronic diseases"* well, which was achieved by the 1980s (IP-11: 10).

4.2.2.2. FIPCO's validated customer segments & relationships

The interviews confirm that the relationship with physicians was of a business-to-business nature (B2B) through their sales force and by using a model of sampling and detailing (IP-1 and IP-8). However, IP-17 makes aware of the fact that sampling activities are constrained by legal frameworks. As of a certain point in time, sampling activities became forbidden in certain countries [IP-17].

IP-1 argues that before the 1980s, the relationships with physicians were not very scientific and not legally framed *(*IP-1). *[So, promoting a drug had no difference compared to promoting, I would say, clothing or whatever… you had the reps back then who, if you like, were 'we take you out to dinner', 'we take you to trips', or 'we give your wife gifts']* (Translated from French IP-1:41).

Two interviewees did not agree with defining the relationship with payers as based on automatic reimbursement (IP-2 and IP-17). IP-17 argues that it is hard to define a generic relationship with payers in the FIPCO since it's tied to each country's regulatory specificities. *"[Maybe it's true what you say about Europe, I'm a little less sure about other countries. You see, automatic reimbursement has always depended on - also the level of the country actually]"* (Translated from French IP-17:12*)*. IP-14 reminds that in the USA reimbursement is not centralized but negotiated separately with each health insurance organization, and not automatically done for every innovative drug. Additionally, reimbursement was not automatic for all new drugs. It might have been described as such in the literature, because *"when you have the first small molecules, of course, they kind of compared to nothing, so that's fine"* (IP-14: 23). Reimbursement was not automatic before the 1980s, but rather simpler or relying on simpler evidence. It is more accurate to define the relationship with payers as formal and superficial.

The results from interviews confirm that the relationship with patients through direct advertisement of drugs existed in the past (IP-6 and IP-1). To this day, direct advertisement of drugs to patients is authorized and practiced in the USA and New Zealand, but it was banned in the rest of the world (IP-1, IP-6, and IP-14).

4.2.2.3. FIPCO's validated key activities

All interviewees agree that in the FIPCO, Big Pharma companies, vertically integrated all their activities. The companies try to keep all competencies and all information inside (IP-8). The model of closed pharma companies*, "as defined by Chesbrough*" was dominant (IP-8: 67). Secrecy was a praised virtue. IP-9 admits that *"when [he] started in [Organization name deleted], it was 'keep all the know-how inside never talk', everything is secret"* (IP-9: 202). Secrecy was seen as a key barrier to enter the industry. In very few examples, the drug's API (molecule) was not even patented to protect the knowledge from leaving the company's walls.

For instance, "*No one knows until today how to manufacture pristinamycin… They kept it inside, they did not patent it, they kept it inside… There is no generic in the world. If Sanofi doesn't produce it, well, I'm sorry, staphylococcus aureus is winning then." (IP-6: 55).*

The in-house R&D activities in the Big Pharma companies followed a strictly *"linear process",* from research departments to development departments, to the drug formulation departments (IP-8:47, IP-9). Drug discovery *"was based on the development of small chemical active compounds that have been synthesized by chemists"* (IP-8: 15). The discovery of a new molecule didn't follow a R&D by design approach. Researchers had a panoply of molecules in refrigerators, on which they tried different things until something worked (IP-17). The R&D activities of Big Pharma companies consisted of experimenting with modifications of small chemical molecules to see if the new adapted molecules would produce any effect (IP-1). IP-8 explains that "*you had a model very simple often open-heart, like a mouse heart. And then you can watch the heart and you add some drug to it and if the heart rate increase, then you knew that the drug had an impact on the heart rate."* (IP-8: 24-25). Drug discovery was a "*phenotypic screening-based approach"* (IP8:47). Phenotypic drug discovery consists in testing molecules in a living animal or cellular model (called pharmacological models) to identify if they generate changes in the phenotype (set of observable characteristics of an organism). Researchers used *"standardized pharmacological models"* (animals) and followed a logic of *"trial and error research"* in which serendipity was a key factor of success (IP8:47, IP-9, IP-17). The downside is that the biological target addressed by the API is unidentified (IP-8).

4.2.2.4. FIPCO's validated key partners

There are some specific circumstances when Big Pharma firms either outsource a specific activity or reach out to collaborate with another Big Pharma firm. IP-1 mentions that before the 1980s all pharmaceutical companies did not necessarily manufacture all their drugs in-house. On some occasions, such as limited capacities of their factories, they outsourced the manufacturing to third parties (IP-1: 17). Unlike the popular beliefs, collaborations between Big Pharma companies happened before the advent of biotechnologies. There were partnership agreements between Big Pharma firms for the purposes of exploiting rights to commercialize drugs in different geographical territories.

Big Pharma firms shared documents on bioequivalence or clinical trials conducted in various countries (IP-9: 16, 28). For instance, *"the Japanese firms that produced, but had no presence in Europe, they bought the exploitation rights in Europe.]"* (Translated from French IP-1: 17).

Dedicated chemical firms were key partners of Big Pharma companies (IP-6, IP-9, and IP-19). They played a crucial role in creating the library of molecules for Big Pharma firms. Dedicated chemical firms conduct the chemical screening, *"because it's too chemical for pharma"* (IP-9: 35). IP-8 explains that chemical screening is the proprietary chemical process developed by these specialized companies to generate a maximum amount of related chemical molecules. The following citation of IP-6 shows how chemical screening is conducted: chemical firms try different chemical reaction to change a molecule's structure by changing its chemical groups (e.g., R1 and R2): "*The screening part happens when they say, 'these are the molecules that we can provide out of this process.'... and this is the main structure with R1, R2, R4, R5, ..., we want R1 to be, I don't know, COOH… It's not a therapeutical screening… they sell their technology… then the pharma company appears in the picture and takes over that technology" (IP-6: 39).*

4.2.2.5. FIPCO's validated revenue streams and cost structure

All interviewees confirm that the revenue stream was based on selling drugs, and that in the past about *"95% of the business was made in the US, Canada, the five big European countries and Japan."* (IP-8: 69). Regarding the cost structure of the FIPCO, the most cost intensive activity were the clinical development parts of R&D process (IP-2 and IP-19). IP-9 argues that "*to make a drug, you need €100,000, but to put it on the market, to be safe, you need ten million*" (IP-9: 26). As a rule of thumb, *"for phase three, that's about 100 million for phase two, it's about ten and for phase one"* (IP-14: 31). Costs of development of all the failed drugs increases the overall costs of R&D (IP-14). besides costs of R&D, there were operational costs (IP-2 and IP-19). Operational costs are costs that incurred after a drug was awarded its marketing authorization, and include manufacturing, supply, marketing, and sales (IP-2 and IP-19). Even though Big Pharma companies invested a lot in the sales force, marketing and sales costs remained ten times less than R&D costs. When defending the market position of the blockbuster against the penetration of generics, cost switched from R&D to marketing and sales (IP-2).

4.2.3. Validation of the IBCO based on expert interviews

The overall opinion of the 16 interviewees about the accuracy of the conceptual IBCO was more heterogeneous. Only three interviewees find the conceptually derived model completely accurate, and the rest (13) judge it to be accurate to some extent. In the following, the results of processing all deviant and non-deviant statements and examples generated thought the interviews are summarized in the validated new IBCO of Big Pharma firms (see Table 10).

In Table 10, contributions to literature on BM of Big Pharma firms are highlighted in grey. The literature on the BM of Big Pharma firms since the advent of biotechnologies did not mention the following important BM elements:

- Offering a bundle of drugs with complementary services is new value proposition in the current BM of Big Pharma firms. Especially by bundling drugs with digital services, Big Pharma firms can better serve the customer segment of patients. Through data exchange and involvement in treatment choice, Big Pharma firms established a new business-to-consumer (B2C) relationship with their patients**.**
- Big Pharma firms engage in hybrid models of value creation (mixture of collaborative and in-house), not only for drug discovery and development activities but also in all other key activities of a drug's life cycle.
- In the IBCO, post-lunch costs are almost as important costs as costs for drug development.

Table 10. Since the 1980s: the validated Integrated Biopharmaceutical Company (IBCO) business model (Source: Own table)

Business model dimensions		**IBCO**
Value Delivery	**Value propositions**	Bundling drugs with complementary services Drugs from chemical synthesis Drugs from biotechnologies (biologic synthesis) Mass indications: Disease with high incidence Niche indications: Disease with low incidence
	Customer segments & relationships	B2B to Payers: Increased direct relationship around discounts and reimbursement of drugs B2B to Physicians: Sampling and detailing model, service marketing B2C to Patients: data exchange and involvement in treatment choice
Value creation	**Key activities**	Hybrid models of drug discovery and development, regulatory affairs, market access, manufacturing, supply, marketing, pharmacovigilance activities
	Key partners	Research organizations, DBFs, other Big Pharma firms, digital technologies companies, KOLs, CROs, CMOs
Value Capture	**Revenue streams**	Selling blockbusters: High volumes, lower prices Selling niche busters: Low volumes, higher prices Price discounts via conditional reimbursement schemes and voluntary licensing agreements Digital services (very rarely)
	Cost structure	Costs for drug development until market launch: - Dominated by costs of clinical trials - New costs of health economics data Operational costs (manufacturing and distribution) Post-lunch costs: - Marketing costs: Complementary services - Pharmacovigilance activities

B2B: Business-to-business B2C: Business-to-consumer
DBFs: Dedicated Biotechnologies Firms; CROs: Contract Research organizations;
KOLs: Key Opinion Leaders; CMOs: Contract Manufacturing Organizations
Segments marked in grey highlight differences resulting from the interviews to Table 5

4.2.3.1. IBCO's validated value propositions

Three main aspects characterize value positions of Big Pharma firms after the advent of biotechnologies. First, drugs are bundled with complementary services. Second, two types of drugs are offered: drugs from chemical synthesis & biotechnologies. Finally, two types of drugs indications are targeted (niche & mass indications). Each of these aspects are described in the following segments.

a) Bundling drugs with complementary services

A main innovation in Big Pharma firms' BM is that *"[i]t's not a product-focused thing anymore. It's more like a comprehensive offering, which is product plus services related to that"* (IP-10: 41). Prescription drugs are bundled with complementary services, so-called "*beyond-the-bill activities"* (IP-10: 77, IP-13 and IP-17). A complementary service is important, *"but it's not really the core of the business"* (IP-27: 37). The interviewees mentioned at least five benefits behind the bundling of drugs and complementary services (see Table 11).

*Table 11. Bene*fits of complementary services for patients, physicians, and Big Pharma firms (Source: Own table)

Benefit	**Ref.**	**Direct quotation**
Improve the interaction between the patient, the doctor, and the company	IP-10	"*The doctor gets the information on the patient directly from the digital ecosystem… the interaction between patient, doctor and the company gets a lot better"* (IP-10: 43).
Create more value for patients and support them to adhere to their treatments and secure the value of drugs.	IP-10, IP-11, IP-13, and IP-17	"*There is always a big problem of adherence or proper use of drugs]"* (IP-13: 35) *"[because afterwards it is quick to say "wait, your drugs don't work.]"* (Translated from French IP-17:23).
Enable patients to better engage with the Big Pharma company	IP-1, IP-10	*"So, if you offer services beyond the product that the patients find valuable, then you can engage them, and the patients like it"* (IP-10: 43).
Create comprehensive solution to support physicians' activities	IP-6, IP-13, and IP-17	*"It's good for the physicians … Instead of having points every three months or every two months, they have basically almost daily results"* (IP-6: 78).
Complementary services enable a company to differentiate their offers	IP-1 and IP-10	*"[for rheumatoid arthritis, you have several players with monoclonal antibodies… the differentiation is on the whole, the product plus the service]*" (Translated from French IP-1: 53).

According to the interviews' data, Big Pharma firms offer at least four types of complementary services: (1) patient support programs, (2) public events, (3) healthcare professionals support programs and (4) pharmacovigilance activities.

Patient support programs (PSPs) are a common type of services provided by Big Pharma companies which are in constant development (IP-1, IP-10, IP-13, IP-19, and IP-27). These services range from technical support, financial support, to tailored trainings and disease management programs (IP1 and IP-17). For instance, Sanofi has a PSP for its drug Lantus® where they explain to the patient how to change the needle and the insulin cartridge in the pen (IP-1). In another example, trained educators go weekly to physicians' practices for a one-hour training with all new diabetic patients (IP-17). Certain PSPs focus on providing access to drugs to low-income patients (IP-1). In Latin America, Big Pharma firms offer drug access assistance programs that track a patient's income and offer (loyalty) programs with discounts on products for low-income patients (IP-1). In Tunisia, Big Pharma companies must provide some of their new drugs free of charge to very low-income patients to get their drugs approved by health authorities (IP-2 and IP-19). All the PSPs are solely financially supported by Big Pharma firms and don't generate direct revenues (IP-1, IP-2, IP-10, and IP-17). All PSP have strategic goals such as ensuring customer loyalty and lock-in effects.

Public events can be in the form of large-scale awareness campaigns or rather small symposia or workshops (IP-1, IP-10, IP-13, and IP-27). Public events are organized for the education of patients or healthcare professionals (IP-13 and IP-27). Public events are useful to raise the public's awareness about diseases and engage them to conduct early diagnostics (IP-27). Through an early diagnosis, the pool of patients eligible for these treatments will increase mechanically. The second business interest is to generate more (and better) evidence (data) about the drugs' efficiency (IP-13). These new data improve drugs' marketing with physicians (IP-17).

Healthcare professionals support programs are an established type of complementary services of Big Pharma firms (IP-13 and IP-19). They organize professional trainings to support physicians in accessing education opportunities thought out their professional life (IP-13). The continuing medical trainings provide updated scientific data to physicians, for a better proximity to available and reliable clinical data (IP-13).

Pharmacovigilance activities provide another guarantee for the physicians about the safe, real-life use of marketed drugs (IP-13). Big Pharma firms are responsible for ensuring drug safety to the best of their abilities. They are active in the detection, collection, assessment, and prevention of side effects of marketed drugs throughout their entire shelf life (IP-13).

Digital technologies enable further complementary services (IP-2, IP-11, and IP-17). For instance, Merck KGaA is collaborating with Garmin Ltd. (digital wearable company) to enhance the value and benefits of their antihypertensive drugs (IP-10). Vital parameters of patients taking antihypertensive drugs are continuously monitored through digital wearables of Garmin Ltd. and are directly shared with patients' physicians to improve the management of their diseases (IP-10). In addition, most Big Pharma companies reach out to their customer segments through new digital channels. They offer various digital services such as websites and smart phone applications (Apps) (IP-10). Some Apps are designed to improve the follow-up of patients, *"so it is actually for the physician's eyes"* (IP-6:78). Other Apps are designed for patients' use about the management of their diseases (IP-6). For Apps associates to drugs against high blood pressure, such messages are displayed: *"Don't stand up very quickly"* and *"If you feel this symptom, call your doctor"* (IP-6: 78). Digital offers can rarely generate direct revenues. Recently, a European health authority reimbursed a Novartis-application that provides patient with personalized coaching (IP-17).

In summary, complementary services offered by Big Pharma firms are of key importance for a better responsiveness of patients to their treatments and providing better healthcare. Better patients' care translates into a higher satisfaction of physicians and their patients which impact positively on drug sales (IP-13). While digital technologies seem to play an important role in the complementary services offered by Big Pharma firms, interviewees remained tacit on the exact nature of that role.

b) Two types of drugs offered (from chemical synthesis & biotechnologies)

Many interviewees affirm that *"the chemical screening remains very important"* for Big Pharma firms (IP-6: 74 and IP-31). The resources allocated to the chemical industry have been significantly reduced (P-6, IP-14, and IP-17). The main difference to the value proposition of the FICPO, is that the rate of producing new chemical molecules is significantly lower in the IBCO (IP-6). Big Pharma firms *"know that there's not as much out there"* (IP-14: 53).

IP-10 explains that there is *"some kind of a ceiling to what you can achieve from a commercial point of view"* with chemical drugs, which explain why their development is forsaken (IP-10: 57). *"You cannot ask for 500 euros for a pack of painkiller, right?"* but you can for a biotechnologies-based anti-cancer drug (IP-10: 57). There is a clear trend to switch their focus on biological drugs based on biotechnologies (P-6, IP-14, and IP-17).

In their Big Pharma firm, IP-6 experiences that 80% to 90% of their business comes from biotechnologies (IP-16). Since the 1980, "*biologic drugs are seen in high potent drugs; that is drugs made for cancer and those kinds of therapeutic areas"* (IP-31: 7). Generally, new biotechnology-based drugs aim to *"target areas that small molecules could not target, could not reach"* (IP-14: 23). Biotechnologies, such as gene therapies *"enables you to address a new disease and also to heal the disease"* and not just to treat symptoms (IP-8: 29). *"It's kind of giving you another level up on the distinct therapeutic value"* of drugs (IP-14: 53). In the IBCO, molecules are either *"first-in-class"* or *"best-in-class"* (IP-31:15). First-in-class drugs are innovative drugs offering a new treatment option through a novel and unique mechanism of action. A best-in-class molecule is not first-in-class, but *"may have improved pharmacokinetic or improved pharmacodynamics profiles… or has lesser side effects"* (IP-31: 15). IP-16 and IP-27 think that biotechnologies are *"changing people's life and the way we manage diseases"* (IP-16: 75). Living with many diseases, like multiple sclerosis or diabetes, or cancer *"required these kinds of technologies, in order to provide… better quality medication"* (IP-27: 5).

In summary, drugs offered within the pharmaceutical industry range from chemical to biotechnology-based drugs (IP-8). Regardless of its type (i.e., chemical of biologic), a drug offered in the IBCO needs to 'get the job done' ("first-in-class" or "best-in-class"), create more gains (almost guaranteed efficacy) and less pains (biologically targeted to generate fewer side effects) for customers. Drugs originating from biotechnologies are more frequently associated with values proposed in the IBCO.

c) Two types of targeted drugs indications (niche & mass indications)

Certain *"small molecules can be as specific as biologics"* (IP-8: 29). In comparison to chemical drugs, biotechnology-based drugs have more targeted indications (IP-6 and IP-14). Biotechnology-based drugs have a higher value than existing chemical drugs, when they outperform them for specific sub-groups of patients (IP-14).

Many mass indications represent completely saturated markets in which only sub-populations (niche indications) remain profitable (IP-6). In fact, biotechnologies enable Big Pharma firms to open their business to markets previously disregarded because of their small patients' population (IP-14). With biotechnology-based drugs, producing an "*orphan drug is a good opportunity"* (IP-8: 23). IP-8 confirms that Big Pharma companies try to address niche indications. Niche indications are very small segments of the overall pharmaceutical market, such as rare diseases, multiple sclerosis, and the multiple niche segments within oncology (IP-10). Niche therapies are a major driver of a company's portfolio development (IP-18). Niche busters describe several recent biotechnology-based drugs specific to patients representing *"maybe one or two percent of an already small population"* (IP-10 and IP-14: 19). The common characteristics of niche indications is the sizable and quantifiable number of patients, who have high access to medicine (IP-10). Niche indications have the favors of Big Pharma firms (IP-14).

"With the biologic drugs, I think if you can still target mass markets, you're still going to target mass markets, right?" (IP-14: 15). Many of the new biologic targets of biotechnology-based drugs, are present in diseases with high incidences (mass markets) (IP-14). For instance, Keytruda® (Pembrolizumab) Merck & Co.'s PD-1 inhibitor, is used alone or in combination with other drugs to treat at least 9 types of cancers (from liver, head and neck, lung, skin, bladder etc.). This drug target mass indication and generates about 20 billion USD a year for Merck & Co. (IP-14). Additionally, IP-14 argued that as biotechnologies developments are moving towards newer technologies such as antibody drug conjugates, and m-RNA modulation, a broader population of patients can be reached.

In summary, the focus on niche and mass indications *"is not an either or"* situation, but both values coexist within Big Pharma firms' current BM (IP-8, IP-18: 21). When technologically possible, larger profitable markets are the logical choice of any company (IP-14). Big Pharma firms offer many value positions which are made of carefully selected combinations of chemical or biologic based drugs, niche or mass indications and types of complementary services. The choice of the value position depends essentially on its expected profitability. In the next section how Big Pharma firms deliver their value proposition to their three customers segments is presented.

4.2.3.2. IBCO's validated customer segments & relationships

Complementary services (in 4.2.3.1.a) deepen the nature of the relationships of Big Pharma firms to its three main customer segments (patients, physicians, and payers) to varying degrees (IP-1). IP-8 refers to the COVID crisis to highlight that Big Pharma firms have, in addition to the B2B relationship with payers and patients, a B2C relation to their patients' groups. It is often hard to discern if a certain service is targeted rather to the patient, physician, or payer. When considering the case of a digital App that allows patients to better manage their diseases, physicians will be able to provide better care, which will result in fewer healthcare costs for payers. Despite this logic, complementary services offered by Big Pharma firms do not have an impact on the negotiation of the reimbursement of their drugs with payers (IP-1). As far as payers are concerned, the quality of a drug is guaranteed since it is approved by the health authorities (IP-10). IP-10 deplores that "*[p]remium price products are not preferred by the payers… the proportion of payers who pay heed to these kinds of extra services and beyond the bill services and patient support programs is not very high in number*" (IP-10: 45).

a) Relationship to physicians

The relationship of Big Pharma firms to physicians is based on the sampling and detailing model (IP-9). Healthcare professionals would say that they are saturated with medical promotion (IP-13). However, the detailing and sampling model shows at least two restrictions. Certain types of drugs cannot be given as samples to physicians (e.g., Methotrexate, a chemical drug for oncology), either because of legal reasons (only administered in a hospital environment) or because it is too expensive to sample (costs more than 1000 Euros) (IP-19). Drugs that are only administered in hospitals cannot be prescribed by physicians in private practices and neither can they be bought by patients at community pharmacies (IP-19). In fact, *"most of the time, biopharmaceutical products, you cannot give them as simple samples"* such as oncology or growth hormones drugs (IP-19: 33). The relationship to physicians is strengthened by the endorsement of the key opinion leaders (KOLs) through different kinds of communication channels (e.g., events, webinars) (IP-19). Big Pharma firms *"really know how to talk to doctors, how to explain things to them"* (Translated from French, IP-17: 25).

In fact, despite their scientific background, physicians face difficulties to fully grasp the scientific background behind an innovative drug (IP-17). Big Pharma firms train their medical sales representatives to popularize and simplify the scientific background that demonstrates the efficacy and safety of their drugs (IP-17).

The relationship between physicians and sales representatives, is highly regulated and has become very scientific (IP-1). According to IP-1, Big Pharma firms are engaging in *"service marketing"*. Service marketing is a marketing model where you offer a service to promote your drug (IP-1). Complementary services have greater influence on physicians' prescription decisions (IP-1). For instance, through PSPs, a company develops a more engaged relationship with physicians than with patients (IP-1). The patient is not aware of the various PSPs and only realizes that such programs exist when his/her physician enrolls him/her in one (IP-1). IP-1 would rather say that it's the relationship with physicians that is mostly positively impacted by the various PSPs associated with Big Pharma firms' drugs. PSPs are one way to create continuous relationships with physicians, since beyond providing access to the drug, Big Pharma firms provide apps to follow up, track and monitor their patients (IP-19). In other terms, PSPs are a direct after-sales client service, with continuous open communication channels for back-coupling of the patient's results with the producer (IP-19). Big Pharma firms dedicate whole teams just to deal with this part (IP-19).

b) Relationship to patients

The term disintermediation as a new form of relationship to patients was not accepted by many interviewees (IP-1, IP-6, IP-13, IP-17, and IP-27). They argue that direct contact with patients is not authorized and can only be possible through the intermediary of healthcare professionals (IP-13, IP-17, and IP-27). Interviewees agree that since the 2000s with the advent of the internet, patients have a bigger role in the BM of Big Pharma firms than they did before (IP-1, IP-6, IP-9, and IP-10). Patients take more responsibility during the management of their diseases, they are more informed, and they compare their treatment options themselves (IP-1, IP-6). Interviewees agree that new digital technologies have changed "*the relationship of the patient with his disease and even of the patient with his doctor"* (Translated from French IP-1: 51). The use of digital technologies is neither for promotion, nor for interacting directly with patients, but for collecting data (IP-13). Big Pharma firms are in favor the involvement of patients in their therapeutic choice (IP-6 and IP-14).

More informed people mechanically increase the overall size of the market (IP-14). Nowadays "*pre-diabetes is accepted as a kind of medical condition"* and the more people are aware of that condition, the bigger the size of the overall diabetes market (IP-14: 39). Increasing the market turns out to be a real competitive advantage for Big Pharma firms who have the resource to invest in the education of patients and well differentiating their products (IP-14). Patients are getting more and more scientifically literate (IP-14). Their decisions remain rationally bound by previous experiences of others or their own risk aversions (IP-14). A natural consequence is that companies try to make sure that data are available to enable patients to be better informed (IP-14). In the example of cancer therapies, patients are presented with available protocols or programs like the ones with targeted gene therapy (IP-6). They are presented with statistical data on efficiency, side effects, and it is up to them to choose their treatment option (IP-6). Certain innovative treatments might require an out of the pocket contribution of the patients to the costs of their drugs. Additionally, Big Pharma firms are in constant need of patients to conduct the clinical trials, part of which informed consent is perquisite (IP-6). *"So, it is a choice because it depends on the payment"*, since innovative therapies might be only partially covered, but also because these therapies could still be at the third phase of clinical trials (IP-6: 80).

c) Relationship to payers

With the advent of expensive biotechnology-based drugs, reimbursement negotiations have become the corner stone that defines the relationship of the Big Pharma firms with payers (IP-2, IP-6, IP-13, IP-16, IP-17, and IP-19). Since payers are more focused on the value of drugs, companies increase their direct relationship to them to prove the value, efficiency, safety, and cost benefits of their drugs (IP9). The intensity and importance of this relationship depend tremendously on the regions of the world (IP-2). The relationship of Big Pharma with payers resides in the tradeoff between a profitable business and lower healthcare costs (IP-11). IP-11 recounts of a personal discussion with a French payer, in which their Big Pharma firm proposed an evidence-based reimbursement scheme. "*You launch your drug, you study the drug and get some end points already agreed at the beginning"* and depending on the evidence, the reimbursement of a drug "*can go upwards or downwards"* (IP-11: 57). IP-11 deplores that for the French payer, even if the results exceed expectations *"the price is never going to go up… It's either readjusting to go the same level or down"* (IP-11: 57).

Historically, the emergence of reimbursement negotiations begins during the last ten years of the classic pharmaceutical industry (1970s) in the USA and in Europe (IP-2). Chemical drugs like clopidogrel (Plavix®, Sanofi) were the first to undergo assessment based on cost effectiveness and the evaluation of their added value comparatively to gold standards like Aspirin® (Bayer), which were 100 years old (IP-2). Cost effectiveness studies become standards in negotiating the reimbursement of new drugs.

Interviewees complain that payers, all around the world, focus more on the cost component of the evaluation rather than the benefits or effectiveness of new drugs (IP-2, IP-10, IP11, IP-16 and IP-17). "*We come with a drug that has good results. But what we hear back is yeah, but you know, there is uncertainty, and this is a biologic, it's expensive so how much is the discount you can give me?"* (IP-11: 12). *"And it is sad to just say it's expensive when no one sees the price of side effects of other drugs and the complications of a bad disease management"* (IP-16: 75). IP-11 alerts that, if public payers don't devise better ways to bring the relationship with Big Pharma firms beyond simple discounts, the firms will turn towards private payers as new customers. A privately dominated healthcare system risks the disappearance of the universal coverage and the aggravation of the inequality of healthcare (IP-11).

IP-11 confirms that *"pharma is ready... I've attended pharma conference, I can hear not just my company but other company, and we're all trying to go to the same direction"* of finding ways to collaboratively deal with the tradeoff (IP-11: 18). The problem is that payers are not showing the same willingness to engage with Big Pharma firms and improve the access of patients to innovative treatments (IP-11). First, payers are not ready for change because they do not have the capability or are repelled by the immensity of the changes necessary to implement innovative procedures (IP-11). Second, they seem to lack the sufficient knowledge or necessary data to make informed decisions about cost effectiveness of drugs (IP-11). Actual data (and not estimates) on costs for different scenarios are not sufficiently available to payers.

In conclusion, physicians remain the most influential customers of Big Pharma firms. Patients have an increasing role in their therapeutic decisions. Payers need to develop more value-based relationships to Big Pharma firms to create more cost-effective drugs. In the following the way Big Pharma firms create value through their activities and key partners is described.

4.2.3.3. IBCO's validated key activities

The key activities of Big Pharma firms remain in essence the same. The value is created by discovering, developing, bringing to the market, manufacturing distributing, marketing drugs as well as monitoring and ensuring the consistency of the quality of drugs throughout their shelf lives. The main characteristics of the key activities of the IBCO are not what is being done, but how it is being done. *"They integrate all from internal and external sources dependently on what they need"* (IP-8: 67). In FIPCO, Big Pharma firms already engaged in some forms of collaborative R&D. However, within the IBCO, they have significantly increased their collaborations in number and breadth of partners, as well as included more international partners (IP-14). Big Pharma firms are creating value through different hybrid models combining in-house and external activities. All the key activities related to drug discovery, development, manufacturing, supply, market access, regulatory affairs, marketing, and pharmacovigilance can be outsourced to some extent (IP-1, IP6, IP-9, IP-10, IP-18, and IP-19).

a) Hybrid model of drug discovery and development

Nowadays, there is no Big Pharma firm that outsources or relies 100% on vertical integration (IP-2). All interviewees' opinions converge that Big Pharma firms adopted a hybrid model for drug discovery and development since the 1980s (IP-1 - IP-31). This hybrid model consists in a complementarity between in-house and collaborative R&D activities (IP-1-IP-31). There is not a single variant of the hybrid model of R&D adopted by Big Pharma firms (IP-2). The hybrid model of R&D is, more accurately, a spectrum, in which the ratio of in-house to external R&D activities varies depending on the strategic orientation of the firm. The spectrum varies from a pseudo-vertical integration to semi-integration. The pseudo-vertical integration consists in conducting almost everything internally with only very limited and intimate partnerships (often with academics) (IP-2). In this variant, the Big Pharma firm is conducting 90% of the necessary R&D activities in house; from pre-clinical to phase 4 of clinical studies (IP-2). The 10% of external activities consist of buying or partnerships of opportunities such as buyout of molecules patents, or regional co-marketing (IP-2). This is often the case for Big Pharma firms that are very focused on a single, or very few therapeutic areas (IP-2). In the case of companies that are in several therapeutic areas, the ratio of in-house to external activities can be up to 50/50 (IP-2).

Activities that are too risky are outsource or bought in (IP-6 and IP-13). Big Pharma firms are not anymore, the ones to take risks (IP-17). They are bound by their need for high profitability and approach research with a 'wait and see' attitude (IP-17). For instance, breakthrough research is no longer done in the labs of Big Pharma firms, but it is bought (IP-17). IP-17 believes that today, new drug candidates are discovered outside the pharmaceutical industry in smaller structures. The small research-focused structures dare more and are agile (IP-17). They have a small number of researchers and a unique objective: Finding an interesting molecule and sell it out to a Big Pharma firm with the highest price possible to sustain their activities for the next years (IP-17). Once a molecule shows real potential (proof of concept), then many Big Pharma firms will fight to buy the successful company that discovered this molecule (IP-17). IP-17 illustrates the cautious attitude of researchers in Big Pharma firms through the recent R&D fail experienced by Sanofi. During the COVID-19 vaccine race, researchers at Sanofi experienced an extreme deception and fail (IP-17). Sanofi' researchers had worked on mRNA technology in the past, and decided to abandon it, while preferring a more traditional and predictable technology for the development of their COVID-19 vaccine (IP-17, Nora, 2021). When a vaccine from Pfizer and BioNTech based on that mRNA technology led the race, Sanofi lost on two levels (Nora, 2021). First, Sanofi lost the vaccine race because until 2021 they did not manage to bring a vaccine to the market (IP-17). Second, its researchers realize that they are no longer the agile and daring ones when it comes to drug discovery (IP-17).

Big Pharma firms outsource activities that are capacity, resources, and time intensive. Companies such as GSK, Pfizer or Novartis outsource certain steps of their research process to certain developing countries, like India or China (IP-31). *"They design their molecules, map it to a target receptor or a protein or whatever, and that structure come to the Eastern countries for synthesis"* (IP-31:25). The costs of the research required to synthetize a new chemical molecule are half as much in India than in Europe and even 10 times cheaper in China (IP-31). Other reasons for outsourcing certain steps of the research process to locations outside of Europe and the USA are related to environmental reasons (IP-31). For instance, certain experiments that are forbidden in the USA by the Environmental Protection Agency are conducted in China (IP-31).

The clinical development part of the R&D process remains in the Western countries because the health authorities expect data form their populations (IP-31).

In sum, the degree of externalization in the hybrid model for drug discovery and development varies from one Big Pharma firm to the other. The logic is to outsource or buy in activities that are too risky (IP-6 and IP-13). Activities that are capacity, resources, and time intensive are outsourced to take advantage of resources of other companies (IP-6 and IP-13). Big Pharma firms save their own capacities and resources for activities with higher impact on their business's growth (IP-6).

b) Hybrid model of regulatory affairs, market access and marketing

Depending on the Big Pharma firm, certain ones choose to outsource most of their regulatory affairs or marketing activities, to third-party service companies (IP-6 and IP-9). These service companies receive key objectives and get paid either per deliverable or per successful drug submission (IP-6). For instance, Creative Ceutic is an independent company that works with many Big Pharma firms on providing health economics data and supporting them with the market access of their drugs (IP-19). Marketing decisions in the pharma industry are data driven based on data analytics and data visuals (IP-19). Certain consulting firms, such as IQVIA provide these kinds of services to most Big Pharma firms (IP-19). In fact, *"today, there's a lot more outsourcing, if the company wants to focus… more on R&D, manufacture better, include new technologies in our processes and, well, regulatory affairs, someone else can prepare the files and file them for us"* (IP-6: 88). IP-10 argues that *"by and large, if a company has a product that's having a global standing, by and large the company will tend to do the marketing themselves, even if they are selling the product through third party organizations"* (IP-10: 47 and IP-19). When a company does not have direct operations in some countries, they operate through the third-party sales organizations or contract sales force (IP-10 and IP-19). The core of the marketing, the marketing strategy is always kept in house even if the operational part is outsourced (IP-10 and IP-19). The same applies for regulatory affairs, where most often the strategic part remains in-house and the operational one is outsourced (IP-10). In fact, IP-13 explains that support functions are also internalized for compliance motives (IP-13). The question of outsourcing *"it's a question of data, it's a question of privacy and a question of trust and it's about the culture in the company"* (IP-19: 43). Consequently, some companies trust third parties which have shown that they are worth that trust through history of collaborations (IP-19).

Big Pharma companies established market access departments, which are based on health-economic models (IP-1). This decision is a consequence of the increased need to provide empirical evidence of drugs distinct therapeutic value and their improved costs-benefits ratio in comparison to standards of treatments (IP-1). So-called active pharmacovigilance and risk management plans (parts of health technology assessment) are new key activities of Big Pharma firms form the 1990s (IP-1). Internally, all Big Pharma firms developed new departments and job description, such as data analytics department or digital officers (IP-13). In the case of bundling drugs with complementary digital services, digital officers at the Big Pharma firm only coordinates (IP-13). They surround themselves with consultants and external service providers (IP-13). And they follow dashboard built on the Key Performance Indicators (KPIs) of the firm to track their activities (e.g., developing animation, administration of social networks) (IP-13).

c) Hybrid model of manufacturing

What is also true for all Big Pharma firms is that they are divesting in-house manufacturing and doing more and more sub-contracting of manufacturing activities (IP1). Very critical parts of the manufacturing process remain internalized unless the equipment for a full-scale production is not available (IP-6). The outsourcing is very common, especially if a company does not want to invest in new equipment, or technologies that only serves a limited number of products (IP-6). Certain parts of the process that are not value intensive (e.g., filling vials with water for injection) are typically subcontracted (IP-6). For instance, a company can prepare their own bulk of the drug and outsource filling the solutions in smaller vials and their packaging to third-parties (IP-6).

The model of extensive outsourcing showed limits and Big Pharma firms are going back to some re-internalization (IP-13). The aim is to find a balance between outsourcing and in-house activities and not to be paralyzed by global supply issues (IP-13). For instance, raw materials are not produced in-house anymore but generally supplied from South-East Asia (IP-13). During the COVID-19 crisis, many Big Pharma firms were in a situation of blockage to supply raw materials (IP-13).

Unlike the FIPCO, in which Big Pharma focus on in-house drug discovery, the new model tends to focus on the commercial aspects of the drugs from the second half of a drug's development all the way through marketing and market access (IP-24).

The strong suits of Big Pharma firms are precisely marketing, health economic assessments, negotiating with payers in many countries and a global distribution network (IP-17 and IP-24). Roughly speaking, IP-1, IP-10, IP-13, IP-16, and IP-17 find that market access and marketing are the core business of a Big Pharma company. While IP-6, IP-17 and IP-19 find that it is manufacturing and supply that are the core competences. IP-1, IP-6 and IP-10 add R&D as core competence. IP-10 and IP-13 are convinced that product launch is a critical substantial key activity for any given pharmaceutical companies. They say: *"there is nothing more important than a product launch…and companies don't mind pumping in money for such an activity… So, drug development is important to get the drug in… But having a great drug does not ensure its success… even the best drug will be as good as its marketing… If the profile is bad, you cannot sell it"* (IP-10: 71, 73). IP-13 confirms that product launch, expertise in therapeutic areas and their key opinion leaders (KLOs) are critical activities for hyper-specialized drugs such as in oncology or neurology.

Nowadays the main competence of Big Pharma firms lies in their coordinating abilities (IP-13). The assets are developed externally, and Big Pharma firms *"know how to adapt it, how to integrate it into the global chessboard"* (IP-13: 89). IP-31 believes that only a small number of the molecules in-licensed by Big Pharma firms in the last 20 years have reached the marketplace. The successful ones know how to spend money effectively and efficiently to bring drugs to the market without doing basic research (IP-31). Certain Big Pharma firms know the market so well that they can know which molecule (developed externally) can have an interesting capital for which country or for which population (IP-17). In IP-31 terms Big Pharma firms are "*more like a brokerage firm rather than… a manufacturing company or, an innovation intensive pharmaceutical operation"* (IP-31: 19). In the following sections, key partners and extend of collaboration agreements conducted by Big Pharma firms are described.

4.2.3.4. IBCO's validated key partners

All interviewees agree that research organizations, DBFs and other Big Pharma firms, are key partners (IP-1 - IP-31). Further partners include KOLs and certain service providers of Big Pharma firms such as contract manufacturing organizations (CMOs), CROs and digital technologies companies (IP-6, IP-13, and IP-19).

KOLs are healthcare professional, such as policymakers, physicians, pharmacists, or researchers, which are well-known in their professional communities and have a certain scientific influence (IP-19). By sharing their objective opinion about innovative treatment alternatives, KLOs can have an impact and change the opinion of health care providers, such as physicians (IP-19). Big Pharma firms collaborate with KLOs by having them as speakers in conferences, where they can make recommendations and introduce innovative drugs (IP-1 and IP-19). KOLs are considered by Big Pharma firms as partners and not as clients (IP-19). Because of issues of conflict of interest, no financial transactions can be made between both parties (IP-19). The partnership with KOLs is a *"business as usual"* practice in the industry (IP-1: 193).

Nowadays, most of pharmaceutical and biopharmaceutical companies rely on CROs to conduct drugs' clinical trials of all phases (IP-19). Most often the clinical trials are part of a drug's clinical development but can also be for bio-similarity studies of generic of biosimilar drugs. For example, for the COVID-19 vaccine, the main part of the clinical trials is made by a CRO. When Big Pharma firms communicate that they are working on the clinical trials they are collaborating with CROs to conduct the studies (IP-19).

CMOs are third-party service provider that have the status of partner because they are listed as an official production site in the drug's file and are inspected by health authorities when the Big Pharma is being inspected (IP-1, IP-6, and IP-19). They are operating as a production site that manufactures drugs (or parts of it) on behalf of a Big Pharma company, based on their knowledge, documents and quality standards (IP-6 and IP-19). They have large scale manufacturing facilities, sometime even equipped with specific biotechnologies, that Big Pharma firms can hire (IP-6). Like with CROs, the Big Pharma firm is the sole owner of the knowledge related to the manufacturing process, and only discloses necessary information for subcontractors (IP-6). It would be very risky for the CMO (bad image and lawsuits) to use a pharmaceutical company's know-how to manufacture similar product for another firm or themselves (IP-6). The partnerships with CMOs revolves around a structured knowledge transfer process and active exchange of knowledge in the case of deviations or rising problems (IP-6). The technical transfer process is a risk-assessment-based approach to evaluate the impact of transferring the production to another site on drugs' quality (e.g., comparing machines) (IP-6).

The exchange of knowledge can be for example: *"They start testing things and then they say that, actually, we're not sure if this product is acceptable or not… the owner of the knowledge can actually step in and say, actually, can you send to me some samples, I can test here and tell you if they are fine or not"* (IP-6: 216). In case of termination of the manufacturing contract all documents are destroyed but a legal relationship still binds both parties (IP-6). For quality, safety, and patient-related activities, or in case of complains, the batch records should be provided by the CMO to the Big Pharma firm (IP-6).

Digital technologies companies are the most recent of the service providers revolving around Big Pharma firms (IP-13 and IP-9). They have various business models (IP-13). The most valuable ones are the companies that monetize their data rather than they services (IP-13). They generate data through their own digital applications and sell it to pharmaceutical companies (IP-13). Data can optimize a drug's use and above all provide a better understanding of the needs of health professionals in terms of complementary services (IP-13). The data providers or data brokers (e.g., IQVIA) are key for Big Pharma firms to orient their commercial team and to adjust their commercial strategies (IP-9). Other digital technology providers are collaborating with Big Pharma firms for the development of digital services or products they bundle with their drugs (IP-6 and IP-10).

4.2.3.5. IBCO's validated revenue streams

a) Selling highly priced drugs

Interviewees confirm that selling highly priced drugs is, currently, the most common revenue model of Big Pharma firms (IP-1 - IP-31). Highly priced drugs are meant for specific markets. More specifically, *"the high-priced product segments are entertained by the US market and the top five European markets and Japanese market and then probably one or two larger markets like South Korea and Australia"* (IP-10: 61). Other than the payers in these handful of markets, payers in other countries will not be able to afford the highly priced drugs (IP-10). Consequently, *"high technology-based products are seldom sold in rest of the world"* (IP-10: 61). For instance, in Latin America, other parts of Africa, or Asia Pacific highly priced drugs are rarely sold (IP-10).

The premium prices associated with new drugs are not just a simple correlation with increases in costs (IP-1, IP-6, IP-8, and IP-10). The price is determined not on a cost-based approach, but rather on a value-based approach. First, a company can ask for premium prices because of the newness of technologies embedded in their drugs (IP-1 and IP-8). For instance, in 2019 Novartis launched a gene therapy called Zolgensma® that cures a certain type of blindness in children (IP-1). Zolgensma® is a one-time treatment that costs about 2 million USD per patient (IP-1 and IP-8). Secondly, companies can ask for high prices for addressing medical needs in niche indications, especially if the market is underserved and the drug is a first treatment option (IP-8). Niche busters follow a logic of *"low volume and higher prices"* (IP-8: 47). This logic applies also for Zolgensma® that is indicated for a rare genetic disease having very few pediatric patients around the world (IP-1). Chemical and biotechnology-based drugs alike can be sold for high prices for niche indications (IP-10). IP-10 mentions that Prestel, a new chemical drug, is sold at a very high price for a niche segment of patients with heart failures. When pricing a drug, a company tries to find a balance between its perceived innovativeness and the willingness to pay of the payers (IP-1). Niche indications have sizable and quantifiable number of patients, who have good access to medicine (IP-10). "*These are the segments where people or payers wouldn't mind spending more amount of money"* (IP-8, IP-10: 59). For example, there is a new drug which is a monoclonal antibody from which you take two injections a year and it will regulate your cholesterol the whole year (IP-1). If payers want it for five patients a year, it be sold for a high price (IP-1). But if payers say that they want to make the most of the population benefit from it, it will be sold for lower price (IP-1). It can vary between 1000 UDS and 5000 USD depending on what the payers want (IP-1). The larger your pool of patients, the cheaper the drug price (IP-1).

The move towards niche busters does not deny that Big Pharma firms still pursue blockbuster revenue model of large volumes and relatively low prices (IP-8). For instance, the COVID-19 vaccine (biologic drug) is not highly priced and is indicated for the adult population of the world (IP-8). With their research team, IP-8 analyzed the top 20 pharmaceutical companies (Big Pharma firms). They found that except three companies, more than 50% of the revenues of top pharmaceutical companies *"depend on blockbusters still, and this is even more than in the past"* (IP-8: 27).

Since the FIPCO, Big Pharma firms continue to target to sell a new drug for one billion (or more) USD in the USA in the first one and a half years (IP-10). Compared to the FIPCO, the real paradigm shift in the money-making logic, is that Big Pharma firms realized that *"by capturing minimal number of patients, they can make quite a lot of money"* (IP-10: 37). *"Of course, every company you would like to sell the product with the highest price possible"* (IP-8: 29). *"What happens if we have hundreds of these kinds of drugs? Are they still willing to pay $2 million per syringe?"* (IP-8: 29). In sum, companies need to find a way to offset the increasing number of targeted therapies at affordable high price (IP-1 and IP-11).

b) Price discounts via conditional reimbursement

Reimbursement schemes are rarely a source of new revenues but rather a mechanism that allows Big Pharma firms to give discounts that secure access to the market and the relationship to payers (IP-2). Pharmaceutical firms can suggest and negotiate various reimbursement schemes with payers to secure their revenues (IP-2). Through the reimbursement schemes Big Pharma firms can provide a form of discount without changing drugs' price (IP-2, IP-11). Since payers conduct a pricing benchmark, having highly priced drugs across countries is very important (IP-1). For schemes such as pay for performance, it extremely rare that a firm get paid more if the drug performs better (more efficient) (IP-2). In his decades in the pharmaceutical industry, IP-2 can only recall five or six cases around the world where a pattern of proportionality of payment to drug's efficacy is applied: *"you get paid more if you are more efficient, and paid less if you are less efficient, and paid normally if you are normally efficient"* (IP-2: 27). Typically, in such a pay for performance model, a Big Pharma firm is paid normally if drugs are working as expected (or better) and less if the efficacy is lower (IP-2 and IP-11).

c) Voluntary licensing agreements

These agreements allow Big Pharma firms to generate some income in countries that are unable to afford highly priced drugs. When payer in a country does not have access to a protected drug because it is expensive or for quantity problem, international agreements allow that payer's country to resort to compulsory licenses to be able to offer the drug to its sick patients (IP-1). The government of that country can ask local manufactures to produce those drugs without respecting the existing patent (IP-1).

Of course, such countries need valid public healthcare rationales (IP-1). To avoid losing markets, certain Big Pharma firms, resort to voluntary licensing (IP-1). It consists in giving, voluntarily, to a local manufacturer the right to manufacture that specific drug, in that specific country at an extremely low price (IP-1). This protects pharmaceutical companies against pricing benchmark in other countries since they continue selling the original drug at its original price in other countries (IP-1). For the developing countries, which have a public health and financial problems, they gain access to the drug at an affordable price and quantity (IP-1). A well-publicized example of voluntary licensing is the drug of Gilead against hepatitis B and C that was sold at only 1% of its price in Egypt (IP-1). They gave voluntary licenses to Indians to make generic drugs at low prices for Egypt and for South Africa and other countries with a big low- or no-income population (IP-1).

d) Digital services

Digital services are very rarely source of new revenues. In Europe, some digital services offered by Big Pharma firms are getting prescribed by physicians and reimbursed by payers (IP-17). For instance, a Novartis App that provides tailored disease management coaching for patients is currently reimbursed. Even payers have understood that just a molecule is not enough, but a 360° around the patient (IP-17).

4.2.3.6. IBCO's validated cost structure

According to interviewees, Big Pharma firms' cost structure is first dominated by the costs for drug development until marketing authorization and market access (including health economics studies) (IP-1, IP2, IP-8, IP-10, IP-14, and IP-19). Post-launch marketing are the second cost intensive activities (IP-1, IP2, IP-8, IP-10, IP-14, and IP-19). Typically, once the product is on the market, companies have a margin of about 50 to 30% (IP-14).

Research costs have increased with the advent of biotechnologies (IP-1). *"Biologic drugs are a lot more expensive to produce"* (IP-14: 15). For instance, *"very complicated, usually not very well understood biochemical steps*" required to reach a drug's purity of 99.99% can make development of the drug much more expensive than all preceding steps of the synthesis (IP-9: 60). Additionally, the trend towards zero risk required by payers, results in increased costs for drugs clinical development (phases 1 to 3) (IP-2 and IP-6).

Clinical trials can be very expensive, especially in the phase 3 where they average 300 to 400 million USD per study (IP-14). For instance, *"Cross side effects, they're not so much analyzed until the '80s or really the beginning '90s… and today it must be"* (IP-2 and IP-9: 30). Today studies differentiate between men and women as well as age segments and concomitant medication (IP-9). For instance, the clinical studies for the COVID-19 vaccine of AstraZeneca distinguish between age segments of women and if they take birth control pills (IP-9). Drugs in development have many phases 3 clinical trials, with different ethnicities and other genetic markers (IP-31). Drugs in development are often compared to gold standard drug in the clinical trials to provide evidence of a distinct therapeutic value (IP-14). Practically, it means that firms need to buy quantities of the comparative drugs to use them in their clinical trials (IP-14). If comparative drugs are quite expensive, their costs will increase the overall costs of the trials very rapidly (IP-14).

Finally, drug development costs are dictated by failure rates of drugs, especially if they occur during phase 3 (IP-1, IP-6, and IP-14). For instance, the success rate in phase 1 of clinical trials is around 10% (IP-14). Currently from more than 10000 molecules screened only one drug gets on the market (IP-14). Failure rates have been increasing in the last 10 to 15 years (IP-14). Since the low-hanging fruits have been picked, it is harder to develop new drugs.

For a product that's already on the market, companies may have to pay royalties to some other company, if the drug has not been entirely developed in-house, for example DBFs (IP-14). Normally, production costs are approximately about 5 to 10% of the final selling price. However, drugs targeting niche indications have more impact on manufacturing costs (IP-9). Because of the small number of users, manufacturing is extremely expensive, since *"nobody in the world will make a huge production line of this"* (IP-9: 56). Distribution costs depend on the country (IP-14). For distribution networks in the USA and Europe costs are manageable (IP-14). But in other countries (e.g., Vietnam), companies need to outsource distribution to local firms, which results in an additional five percent of the selling price (IP-14).

Biotechnology-based drugs not only cost more to be developed but also to be sold (IP-16). Nowadays the marketing of Big Pharma firms is more aggressive and more scientific (IP-1 and IP-6). They dedicate more resources for marketing than in the past, for instance for the organization or sponsorship of symposia and conferences (IP-6).

The service marketing of *"beyond the pill activities… can be very expensive too"* (IP-10: 77). The innovative ways to engage physicians, payers, and patients (e.g., PSP) comes with spending enough money on them (IP-10). Since complementary services are, very seldom, a new source of revenue, they generate additional costs for the Big Pharma companies (IP-1). All together, "*the post-launch medical activities… are very important*" (IP-10: 75). Considering that a company detains exclusivity for its drug (patent not expired), new clinical data are still generated (IP-10). The clinical data serve to keep the medical activities up to date and maintain the product's sales post-launch (IP-10). The resources dedicated to marketing serve to present these companies as key partner for research and promotion of scientific knowledge and to keep them anchored in their target KOLs communities (IP-6).

Finally, firms are required to conduct themselves or be responsible of the pharmacovigilance activities of the drugs they have in the market (IP-2 and IP-6). Pharmacovigilance activities aim to monitor (1) the advent of new adverse effects, and (2) the concordance between efficacy results from clinical trials (phase 3) and real-life efficacy results (IP-2). Conducting pharmacovigilance activities (phase 4 of clinical trials) is increasingly expensive (IP-2). So, the costs of pharmacovigilance activities are costs that start with the commercialization of the drug and remain during its whole shelf life.

4.2.4. Collaboration formats of Big Pharma firms in the IBCO

The Table 12, describes all collaborations in which Big Pharma engage, in the frame of their current BM. The collaboration formats colored in grey are formats that have not been discussed in Table 6.

This research found that mergers between a Big Pharma firm and DBF are hardly imaginable because of the significant size difference (IP-14 and IP-24). "*There's no way a big pharmaceutical will lose half of their bargaining power with small biotech firms*" (IP-24: 57). Moreover, mergers between Big Pharma firm and research organization are extremely unlikely because of legal reasons (IP-14 and IP-24). *"The state of Texas is not going to let you take over MD Anderson Cancer Center"* (IP-14: 67). Finally, it is very hard to conceive that a Big Pharma firm will invest, with its corporate venture arm, in research organizations or another Big Pharma firm (IP-14 and IP-24).

Table 12. R&D collaboration formats of Big Pharma firms in the IBCO (Source: Own table)

		Formats	Examples
Collaboration partners	**Research organizations**	Licensing	AstraZeneca / Oxford University (2020)
		R&D contracts	Novo Nordisk / MIT
		Joint R&D contracts	Bayer / German Cancer Research Centre (2008)
	Dedicated Biotechnology Firms (DBFs)	Licensing	Pfizer / BioNTech mRNA technology platform (2018)
		R&D contracts	(No example provided)
		Joint R&D contracts	Pfizer / BioNTech COVID vaccine (2020)
		Corporate venturing	Merck Capital Ventures (Merck & Co., 2000)
		Acquisitions	Roche / GenenTech (1990)
	other Big Pharma firms	Co-marketing agreements	Novo Nordisk and MSD (Japan)
		Licensing a drug	(No examples provided)
		Selling drug's IP rights	Novo Nordisk and Sanofi
		Selling IP rights of drugs' portfolios	GSK and Novartis
		Supplier makership contracts	GSK and Sanofi (COVID vaccine)
		Joint R&D contracts	Merck KGaA and Pfizer
		Join ventures	Bristol Myers Squibb and Sanofi
		Mergers	Astra, Zeneca = AstraZeneca (1999)
		Acquisitions	Pfizer / Wyeth Pharmaceuticals **(**2000)
		Spinoffs	Abbott → Abbvie
	Consortium model		(AstraZeneca, GSK, and Johnson & Johnson) / (Cambridge university, Imperial College London and University College London)

Segments marked in grey highlight differences to Table 6

4.2.4.1. Collaboration with research organizations

Big Pharma firms are concluding R&D contracts with research organizations for right of first refusal. The right of first refusal allows Big Pharma companies to be the first to inspect the output of the funded research and accept or refuse to license it before any other party (IP-1).

Simply put, they have the right to be the first to decide if the new knowledge is of any interest for them and wish to engage in other collaboration agreements (e.g., licensing) (IP-1). Big Pharma firms will support or sponsor whole chairs at universities or whole research centers for many years in exchange of having a 'right of inspection' on the outcomes of the research they are funding (IP-1, IP-27). For instance, Novo Nordisk is developing a new technology for its insulin with a research team at MIT called the smart insulin (IP-2 and IP-27). Based a micro-engineering, nano-engineering systems rather than biotechnologies, the smart insulin will be delivered via oral route, and is active when glucose is high in the blood and is inactive when glucose is not high (IP-2 and IP-16). The system was clearly done by MIT, with grants from Novo Nordisk, implying that at some point they will buy the technology (IP-2). In some cases, the research outcomes are not patentable, and licensing is not a via collaboration pattern. The scientists will delay publications by three to four years to give the company supporting them a first market advantage based on the new knowledge (IP-14).

IP-14 notes that through the R&D contracts, Big Pharma firms are moving further upstream the knowledge spectrum. IP-14 explains that nowadays if knowledge is already published, *"its kind of could almost be too late"* (IP-14: 27). Big Pharma companies try to gain access to the source of new knowledge (researchers) rather than just its outputs. They can have innovation centers, where they group smart scientists, give them resources and hope that they invent or find something worth publishing in high impacted journals (IP-14).

4.2.4.2. Collaboration with DBFs

DBFs are very scientific but they do not have this market analysis competence that Big Pharma firms have (IP-17). Big Pharma firms' unique competences in marketing, health economic assessments, negotiating with payers in many countries and their global distribution network are what DBFs seek through their various partnerships (IP-17). As a Big Pharma firm, you are *"kind of being the big guy that they want to partner with later on… the partner of choice because you have this commercial infrastructure"* (IP-14: 27). All the pharmaceutical companies currently have R&D contracts with small DBFs based on a right of first refusal (IP-1). The right of first refusal allows a Big Pharma company funding a DBF's research to be the first to inspect their molecules and accept or refuse to license them, before any other party (IP-1).

4.2.4.3. Collaboration with other Big Pharma firms

Collaborations between Big Pharma firms remain very commercial agreements that are linked to the portfolio strategy of each company (IP-2). Big Pharma firms that are listed on the stock exchange markets do not present a special financial risk (IP-2).

Many interviewees confirm the existence of licensing agreements between two Big Pharma firms (IP-1, IP-2, IP6, IP-10, IP-14, IP-9, and IP-17). They are probably missing from the literature for at least two reasons. First, some are not disclosed, so nobody talks about them even if they are very common (IP-9 and IP-31). For instance, around the mid-90s, there was a big market on Ginkgo Biloba (IP-9). At least a dozen brands commercialized this drug, but all the molecules come from a unique company called Schwabe, in Karlsruhe (IP-9). The information was not public since every company promotes the distinct value of its drug over the competition (IP-9). No company interfered or made this information public to retain their market shares. In fact, some agreements are done informally, *"on the golf course: 'This is my market, and this is yours... And if you are definitely in this market, I'll hit you back in the other market'"* (IP-9: 154). Second, some of them are just business as usual and are probably not even disclosed in annual reports (IP-8). They would not communicate about it because some of the licensing happening is considered as very common practices (IP-17).

a) Co-marketing agreements

They are very common for Big Pharma firms (IP-2 and IP-17). They are arrangements in which companies will sell competing drugs in their preferred markets and license some of their drugs to competitors for other markets (IP-2 and IP-17). For instance, Pfizer would rather sell drugs in the USA, because it is at home and will license the drug to Sanofi to sell in Africa and Europe for their more favorable market access (IP-2). Moreover, Novo Nordisk in Japan has such a co-marketing contact with MSD (IP-17). For the commercialization of its first biologic drug in Asthma, Amgen[iv] engaged in a co-marketing agreement with AstraZeneca (IP-11). Amgen will commercialize the drug in North America and AstraZeneca will commercialize it in the rest of the world (IP-11). AstraZeneca was a preferred partner due to their leading position in therapeutic area of Asthma and its strong presence in Europe (IP-11). In the frame of co-marketing agreement, licensing allows each Big Pharma firms to benefit from the strong presence of the other in specific geographical area (IP-11).

According to IP-31, this type of agreements stem from the weaknesses of firms in certain markets. The partners are *"trying to cover up the gaps or the weaknesses of each other… those kinds of agreements are borne not by design, but out of the utter necessity to survive*" (IP-31: 25). In this context survival means getting the maximum return on investments and generating the highest revenues possible (IP-31). When a Big Pharma company has done investments to create a new drug, got it approved by heath authorities, but does not have real access to the market, the drug cannot be sold (IP-31). To have access to certain markets, even Big Pharma firms need to collaborate with somebody who is going to give them that access (IP-31). IP-31 believes that co-marketing contracts between European pharmaceutical companies and American pharmaceutical companies are further motivated by political reasons. Because of the known rivalry between European and American Big Pharma firms, politics restrict the access of foreign companies to their home markets (IP-31). These restrictions necessitate that European and American Big Pharma firms collaborate to access each other's markets (IP-31).

b) Licensing a drug

Licensing can be an exclusive or non-exclusive agreement. Novartis or Sanofi manufacture the vaccine for BioNTech/Pfizer is an example of big pharma firms' non-exclusive licensing agreements (IP-6). The licensor shares the information about how they scale up and can send the concentrated vaccine bulk and licensees will dilute it, formulate it, and then fill it in vials (IP-6). Exclusively licensing a drug from one Big Pharma firms to another is a less frequent practice in the industry (IP-1). Licensing often happens at early stages of drug's development cycle (pre-clinical or phase 1) (IP-14). The later the licensing the more expensive it gets (Ip-14). One company cannot develop all the molecules they discover, which does not mean that the molecules have huge liabilities (IP-14). A technology or target molecule can be discovered that has potential, but the company does not aim to commercialize them (IP-1, IP-2, IP-16, and IP-17). In some other cases, the research project might be abandoned for strategic reasons, but some drug candidates have already been found (IP-18). Additionally, having two drugs in the same (or similar indications) is unwise in terms of marketing strategy, since it is impossible to differentiate, and one will cannibalize the other's market share (IP-1). It is beneficial, to generate some returns on investment, to license or sell IP-rights of unwanted biotechnologies and molecules (IP 1, IP 14, IP17 and IP-18).

Since these events are not planned and of a sporadic occurrence, the financial benefits are not considered revenues for Big Pharma firms (IP-14, IP-17, and IP-18). When a company develops two similar molecules and they keep one and give the other, the royalties generated are the benefits of licensing the second molecule (IP-1 and IP-14). Of course, the molecule that is judged less attractive will be licensed-out (IP-1). This collaboration bores the risk of losing market shares and reduced incomes if the Big Pharma firm that in-license the molecule is better at commercializing the drug (IP-1). There is also *"kind of a risk of looking stupid*", when the licensed molecule or technology "*becomes the next big thing*" (IP-2, IP-14:101). The criteria for partner selection arise from the wish to ensure the success of the out-licensed molecule because of the royalties (IP-1). Consequently, Big Pharma firm to whom to license the second molecule should have experience in the therapeutic area, and the drug should complement its existing portfolio (IP-1). Second the company should have the financial resources required to conduct clinical trials and to transform the molecule into a drug (IP-1).

c) Selling drug's IP rights

This is a situation when a Big Pharma firm cedes the whole rights for its technology to another one. This partnership is a rare event but not completely uncommon (IP-18). For instance, Sanofi bought the IP rights related to the discovery of type of insulin (analog insulin) from Novo Nordisk (IP-2, IP-16, and IP-27). Novo Nordisk discovered a new technology leading to producing two molecules of insulin analogs (IP-2 and IP-27). They judged the first molecule candidate more promising than the second one, since is showed better therapeutic quality (IP-2, IP-16, and IP-27). Two molecules are commercialized (IP2). Sanofi commercialized Lantus and Novo Nordisk commercialized Levemir (IP-2). Against Novo Nordisk's expectations, Lantus became the market leader with 70% of market shares (IP-2 and IP-16). Incidentally, Levemir is taught to management students as a case of big launch fail (IP-2). More often the selling of IP-rights happens when a molecule discovered does not fit the company's portfolio or target indications (IP-18). For instance, Novo Nordisk discovered, by chance, a molecule for the treatment of depression called paroxetine (IP-27). Since the new molecule targeted a therapeutic area in which Novo Nordisk had no ambitions, they sold their IP rights to another company (IP-27). Deroxat® (API: paroxetine) is commercialized by GSK.

d) Selling IP rights of drugs' portfolios

This is very frequent practice (IP-2). It consists of a transfer of complete portfolios of a therapeutic area from one company to another (IP-2). A company get rid of a portfolio when deprioritizing or leaving a therapeutic area (IP-2 and IP-14). They acquire new portfolios in therapeutic areas where they want to strengthen themselves (IP-2). For instance, AstraZeneca ceded her diabetes portfolio to Boehringer Ingelheim (IP-2). When Novartis wanted to focus their business only on the therapeutic area of oncology (IP-6), they sold their entire vaccine drugs' portfolio to GSK (IP-6). The collaboration between the two started with GSK buying a concentrated vaccine bulk again Tuberculosis from Novartis (IP-6). Then in 2016, the collaboration transformed, and GSK bought the whole site producing that vaccine bulk from Novartis along with their vaccine portfolio (IP-6). Selling portfolios between Big Pharma firms is a very rapid process (IP-2). It's very often between one and three years (IP-2). Since it is done at strategic level (the CEO level) and tied to portfolio strategies, CEOs are in a rush to get rid of portfolio transfers (IP-2).

e) Supplier makership contracts

They are forms of collaboration, in which a Big Pharma firm is a supplier of another Big Pharma firm. The knowledge exchanged is high even if not all information is disclosed (IP-6). In this type of collaboration, manufacturer and supplier are working together to adjust the power and the formulation of their final product (IP-6). Two Big Pharma firms can collaborate on the development of a complex drug that would require a combination of two technologies. For instance, Sanofi and GSK collaborate for the development of a COVID vaccine (IP-6). Sanofi will provide the antigens (API) and GSK will supply the adjuvant (IP-6). Adjuvants are not the API but influence the clinical response level of drugs (IP-6). Especially in the case of vaccine, the technology in the adjuvant is of key importance (IP-6). GSK adjuvant is a liquid that contains boosters which provide faster or better immune responses (IP-6). This collaboration is beyond the simple supply of the adjuvant as of the early steps of the drug's development until clinical trials (IP-6). GSK will conduct new research on their existent adjuvants to improve and adapt them just for the COVID antigen of Sanofi (IP-6). The highest risk of such a collaboration is to lose an entire drug which is already on the market because of quarrels with that strategic supplier.

f) Joint R&D contracts

Joint R&D contracts between Big Pharma firms are increasing in frequency (IP-10). Big Pharma firms can enable *"better brain-power"* through the synergies of their own *"brain-powers … when it comes to drug discoveries"* (IP-10: 49). *"Every company has a limited amount of money that they can spend on development, no matter how good they think the molecule is"* (IP-14:71). By bringing a partner in the project, a company increases the overall money invested and can develop more research areas (IP-14). However, the value will also be shared with the partner (IP-14).

Joint R&D contracts rarely aim at the development of joint new molecule (IP-1). They are typically at later stages of drug's development cycle (phase 2 or phase 3 of clinical trials) (IP-14). Frequently, the join R&D contract is a co-development and co-commercialization agreement, where both parties are splitting the research and the commercialization part (IP-10 and IP-14). For instance, Merck KGaA is conducting a joint R&D collaboration with Pfizer for the clinical development of its drug Bavencio (IP-10 and IP-18). Bavencio is a biotechnology-based molecule targeting a niche indication in oncology (IP-10). Pfizer is conducting the clinical trials in the USA and Merck is conducting them in Europe (IP-10). They share clinical data, costs, as well as risks (IP-10). Marketing rights of Bavencio are lying with Pfizer for the USA and with Merk KGaA for Europe and rest of the world (IP-10).

In other cases, Big Pharma firms collaborate for the development of a new therapeutic option that combines a drug of each of them (IP-1 and IP-14). The example is an oncology product, which is a combination of two existing products of Merck KGaA and Novartis (IP-19). Each drug alone is not as effective as their combination (IP-1). The advantage is that there is no cannibalization, but a synergic effect (IP-1). The contract is also necessary to access the dug of the other Big Pharma firm (IP-14).

g) Joint ventures

Joint ventures between two Big Pharma firms are an organizational form of collaboration that facilitates co-development arrangements (IP-1). Sanofi and Bristol Myers Squibb created a joint venture to co-develop and share profits of two of Sanofi's drugs: irbesartan and clopidogrel (IP-1). Clopidogrel was called Plavix® by Sanofi and Iscover® by Bristol Myers Squibb, while irbesartan was called Aprovel® by Sanofi and Avapro® by Bristol Myers Squibb (IP-1).

For such collaborations to work, teams at all levels of the companies need to have common incentives (IP-1). The previous experience and established expertise of the partner (e.g., Bristol Myers Squibb) in the therapeutic area is paramount for the success of such a co-development collaboration (IP-1). Having a partner who already knows opinion leaders, for example, or key researchers for clinical studies in the targeted disease is most important when entering a new therapeutic area (IP-1).

h) Spinoff

A lot of Big Pharma companies are moving towards a spinoff model, such as Abbot, Pfizer, and Sanofi (IP-13). Abbott split its innovative activities and founded AbbVie which specialized on specialty care (in 2013) (IP-13). In the case of Pfizer or Sanofi, the model consists in concentrating on products with high profitability, and spinoff products with low profitability to be managed separately (IP-13). Sanofi has Sanofi Specialty Care focusing on innovative drugs and Sanofi Consumer Health Care focusing on OTC products (IP-13). Pfizer Consumer Healthcare is an independent entity that is more specialized in mature products. In 2019, Pfizer Consumer Healthcare (49% of shares) merged with GSK Healthcare (51%) to form a new company called GSK Consumer (IP-6). The separation of the innovative and less innovative activities of Pfizer was very timely (IP-6). By clearing out the unnecessary branches, Pfizer can focus better on biotechnological products and reallocate resources to more innovative projects (IP-6). That is how they succeeded in being the first Big Pharma firm to commercialize a COVID vaccine (IP-6).

4.2.4.4. Consortium model

It is model somewhere between strategic investment and a kind of philanthropy (IP-2). For instance, there is a collaboration between 3 Big Pharma firms (AstraZeneca, GSK and Johnson & Johnson) and 3 British universities (Cambridge university, Imperial College London and University College London) for the development of new drugs (Ward, 2016). The big pharma firms provide financing and expertise in exchange for a right of first refusal (Ward, 2016). Another example is the case of four Swedish and Danish Big Pharma firms (including Novo Nordisk, Lundbeck, and Coloplast) that are, together, subsidizing many Swedish and Danish research centers (IP-2). Their financial support is not for the development of specific drugs but to develop a strong Scandinavian research ecosystem that can either provide them with researchers or with research results (IP-2).

The risk of such a collaboration format is above all an economic risk (IP-2). The absence of a right of governance of this financial investment put the consortium in a risk of failing to generate basic research which can have applications for drug development (IP-2). Most of the time the consortium funds clear projects over a defined period (IP-2). The funding can stop, if the project is unsuccessful or if the strategic directions of the companies change (IP-2). Another risk is if the research results are good and there is a patent and possibility of successful commercial exploitation, there could be disputes over property rights even if they are already defined in the collaboration contract (IP-2).

4.2.4.5. Benefits and risks of Big Pharma firms' collaborations

The risk and advantages of the various collaboration formats (described above) can be summarized in the Table 13. Many interviews emphasized that a major advantage of collaborations, especially with other Big Pharma firms are sharing development costs and risks. Sharing investments in R&D and sharing incomes is an easier rational decision than going alone at the risk of losing everything (IP-2 and IP-10). Collaboration decisions follow a risk management logic as well as stock market logic rather than a purely economic logic (IP-2). Furthermore, collaborations improve the brand image of Big Pharma firms (IP-6). The sharing of knowledge implied in collaborations, projects the image of Big Pharma firms being the heroes that are willing to create alliances to save more lives or improve patients' quality of life (IP-6). Synergies of R&D capabilities for drug discoveries are specific advantages of joint R&D contracts between Big Pharma firms (IP-10).

From a risk perspective, common risks are incompatibility of teams (IP-17), patent quarrels and harmed reputation or brand imagine (IP-14). In general, information leaks or information spillovers are not a preoccupying risk for Big Pharma firms (IP-6). In Big Pharma firms, uncodified knowledge is dispersed over several departments and even countries (IP-6). Consequently, R&D collaborations don't result in significant knowledge spillovers since no team has the full picture (IP-6). However, patent quarrels are a high risk of R&D collaborations (IP-1 and IP-2). Partners could quarrel about the sharing of the patent rights, especially if new technology resulted from their collaboration (IP-2). The party who has less claims to the rights with have most interest in challenging the claims of the patent holder (IP-2).

The patent holder tends to negotiate an agreement with their partner even if they know they are 100% right (IP-2). Patents quarrels happen typically in partnerships that don't have strategic motives (IP-2). Other types of patent quarrels can be a non-respect of the license in its duration, in its territoriality, in its value (IP-2). Partnerships can have negative impact on teams' motivation (IP-17). For instance, in the case of co-marketing agreements between two Big Pharma companies, the sales team of company A are demotivated because they are forced to sell the drugs of a competitor (IP-17). Or teams are demotivated when a drug discovered internally is then licensed to another company, which will bring it to the market (IP-14).

Table 13. Advantages and risks of Big Pharma firms' collaborations (Source: Own table)

		References
Advantages	Improve firm shares; Announcement effect	IP-2
	Improve brand image	IP-6
	Fill drug's portfolio	IP-2
	Fill a drug's pipeline	IP-2
	Secure global presence	IP-11, IP-10, IP-14, IP-31
	Enter new therapeutic area	IP-11
	Strategical refocus (Hyper-specialization)	IP-6
	Secure some return on investments	IP-1, IP-18
	Share development costs and risks	IP-1, IP-2, IP-10, IP-14, IP-18
	Shorter time to market	IP-1
	Synergies of R&D capabilities	IP-10
Risks	Patent quarrels	IP-1, IP-2
	Compatibility of partnering teams	IP-1, IP-14, IP-17
	Lowering team's motivation	IP-14, IP-17
	"Looking stupid risk"	IP-1, IP-14, IP-18
	Harmed reputation	IP-6, IP-14
	Production disruptions and new R&D costs	IP-6
	No clarity about where liabilities lie	IP-6

Finally, it is of great importance that the potential partner is solvable and benefits from a good reputation especially with health authorities (IP-6). Big Pharma firms do their due diligence before entering any partnership (IP-2). It is also of equal importance that the partner can comply with the Big Pharma firm's quality criteria (IP-6). The potential of the molecule for improving patients' health remain the most important criteria for R&D collaborations (IP-17).

In conclusion, this fourth chapter presents an accurate and detailed representation of the traditional and current BMs of Big Pharma firms (FIPCO and IBCO). One fundamental aspect of the IBCO, which is the different formats of R&D collaborations, has also been explored with examples from the practice. As shown in this chapter, digital technologies are a second fundamental element of the IBCO. While the qualitative interview study provided many insights in the implication of digital technologies in the current BM of Big Pharma firms, the specific types of digital offers remain unpraised. Hence, the next chapter explores the types of value positions in the current BM of Big Pharma firms that involve digital technologies.

5. Digital Value Delivery in the IBCO Business Model

This thesis explores how Big Pharma firms accommodated biotechnologies in the design of their current BM (IBCO). In this chapter, specific aspects of the IBCO that relate to new value propositions and customer segments and relationships, are explored empirically. As potentially disruptive technologies, biotechnologies bring a new value proposition to the industry. The way this value is delivered to target customers is based to some extent on digital technologies. While digital technologies are not (yet) potentially disruptive for pharmaceutical companies, they play a role in the value proposed and delivered to their customers. As seen in the validated IBCO (chapter 4), digital devices and channels are an integral part of the value prosed by Big Pharma firms. Digital technologies enable Big Pharma firms to further bundle their drugs with complementary services for a higher quality of healthcare services. The following questions remain:

- Are there significant differences in value positions enabled by digital technologies?
- Are there significant differences in how values behind biotechnology-based drugs are delivered to customers segments?
- If digital values proposed and delivered to customers are different, where do differences lie?

These differences contribute to better understand how Big Pharma firms accommodated potentially disruptive technologies in the design of their BM. To answer these questions, all digital offers of all Big Pharma firms can be explored though classification methods. Data are structured and grouped in distinct groups of value delivery: i.e., fixed combinations of value positions and customers segments and relationships. In fact, classification methods are important to advance research on building theories on BM (Lambert, 2015). In the BM literature, many attempts to classify BM elements don't use systematic classification approaches (Baden-Fuller & Morgan, 2010; Lambert, 2015). Cluster analysis figures among the systematic classification methods suggested for BM research (Lambert, 2015).

In summary, this study aims to specify the digital value delivery dimension in the IBCO BM. This study does not aim to uncover potentially disruptive value positions.

The cluster analysis method is used to structure data relating digital offers of Big Pharma firms into different groups of values delivered to customers.

In 2019, Tangour et al. (2019) were the first to observe what type of digital products and services are commercialized by Big Pharma firms. The observed digital offers have been clustered in four digital BM patterns which are presented in Table 14.

Table 14. Digital BM patterns of Big Pharma firms (Source: Own table based on Tangour et al., 2019)

Name of the BM pattern	**Firms number**	**Digital offers number**
Sell Digital Products to Health Professionals for Diagnostics	4	10
Free Disease Management Platforms developed with Partners	5	7
Free Apps for the Prevention of Diseases	3	7
Free Apps to Support Patient's Treatment	4	7

This first explorative study has many limitations that require further empirical explorations. First, the authors choose a hierarchical clustering algorithm (Ward method) to cluster the data as it has been applied in other studies (Camisón & Villar-López, 2010; Morris et al., 2013). The argumentation for the use of the Ward method is absent from the paper (Tangour et al., 2019). In fact, non-hierarchical clustering algorithms (e.g. K-means) have also been successfully used by BM researchers (e.g. by Täuscher & Laudien, 2018). Literature confirms that "*clustering is often performed using both hierarchical and non-hierarchical methods to minimize the impact of the limitations of each method*" (Lambert, 2015, p. 55). Consequently, a new study, in which the choice of the clustering method is based on sounds scientific arguments or methods can provide more reliable insights.

A second relevant limitation is the absence of two out of six clusters from the interpretated BM patterns (Tangour et al., 2019). The authors argue that both excluded clusters were not interpretable and did not build a coherent BM, without providing possible explanations (Tangour et al., 2019). Better clustering results are often linked to low ratio of the number of variables to the number of objects. In Tangour et al. (2019), 13 variables are used for the clustering of 53 objects. In fact, the choice of the variables used for the clustering is a key factor in the cluster analysis method (Lambert, 2015).

While a larger number of variables reduces researcher's bias, less relevant variables for interpretation might be statically dominant, which is "*statistically valid but may not be intuitively sensible or useful" (Lambert, 2015, p. 53).*

The current study takes into consideration the main findings and mitigates methodological limits of the study conducted by Tangour et al. (2019). In the following the methodology of cluster analysis is detailed and results are presented.

5.1. Methodology: Cluster analysis of secondary data

This chapter studies digital technologies that are embedded with prescription drugs commercialized by Big Pharma firms. The method of cluster analysis is used to understand data on Big Pharma firm's digital offers. In this study, the whole population of Big Pharma firms is studied and data about all their digital offers are collected. No sampling is conducted. This explorative study relay on data extracted from secondary internet documents that are quantitatively grouped into distinct clusters. The details of this methods are presented in the following sections.

5.1.1. Population studied and data collection strategy

In general, researchers collect data on a sub-set of a population called a sample, hoping to generalize the characteristics observed to the target population (Mazzocchi, 2008). As mentioned above, in this chapter the whole population of Big Pharma firms is studied. According to the definition adopted for this thesis (pharmaceutical firms with revenues greater than 10 billion USD), the population of Big Pharma firms consist of 22 firms. The target population is further segmented into 17 traditional Big Pharma firms and five recent ones (see Tables 2 and 3 in chapter 2).

The objects of this study are the digital products or services offered by Big Pharma firms. No database was found that listed all digital products and services of pharmaceutical companies. Sources available on the internet contain a plethora of data in both volume and variety (Jain, 2010; Xu & Wunsch, 2005). Therefore, the 22 companies' websites, digital stores for smartphone applications (Apps), i.e., Google Play Store (Android apps) and Apple App Store (iOS apps) and practitioner magazines such as MobilHealthNews were screened to identify digital offers of Big Pharma firms.

To extract only relevant data from internet sources, a coding system was developed (see Table 15). The corresponding definition of the sub-codes can be found in Annex 5. The sub-codes are designed in a way that for each object only one sub-code per code exists. The data are extracted based on a binary coding in Excel (1, 0). The digit 1 is attributed for the presence of a variable (sub-code) in the digital offer and the rest of the sub-codes in that code are attributed 0 for their absence. Even though data are numerical, they are not quantitative data but so-called qualitative variables (e.g., the variables "gender" or "marital status") (Rädiker & Kuckartz, 2018).

Table 15. Coding system used to extract data on digital offers of Big Pharma firms (Source: Own table)

Codes	**Sub-codes**
Market type	Prescription drugs
	Over-the-counter drugs
	Medical devices
Value proposition - Degree of digitalization	Purely digital service
	Combined products
	Digitally enabled
Value proposition - Patient Journey	Prevention
	Diagnostic
	Treatment
	Healthcare measures
	Clinical research
Value proposition - Targeted drugs indications	Niche indication
	Mass indication
Customer segments- Direct users	Patient
	Potential Patient / general population
	Physician
	Patients and their social system
Customer segments: Data shared with users	(potential) Patients only
	Health professional only
	(potential) Patients and their social system only
	(potential) Patients and health professional only
	All of the above

The first version of the coding system was developed a priori of starting the data collection. During data collection, some new codes and sub-codes are added inductively if categories were deemed to be missing. To ensure a lower degree of subjectivity, three independent researchers extracted data form internet sources.

When researchers disagreed on objects' coding, contentious objects are marked and reexamined during update meetings. Discussions on contentious objects are interrupted only when:

- a full consensus on an object's coding is reached or
- conclusion is reached that the coding system need to be updated to account for the emerging nuances in the data (inductive approach mentioned above).

Any modification of the coding system requires a full consensus among the researchers. When the coding system is changed, previously coded objects are re-coded.

As Table 15 shows, there are three subcodes that are not related to the definition of a BM: Prescription drugs, OTC drugs and medical devices. Their presence in this coding system is important for data extraction. Since this work only focus on prescription drugs of Big Pharma firms, objects outside this sub-population of digital offers are excluded from the sub-sequent cluster analysis.

5.1.2. Data analysis: Cluster analysis

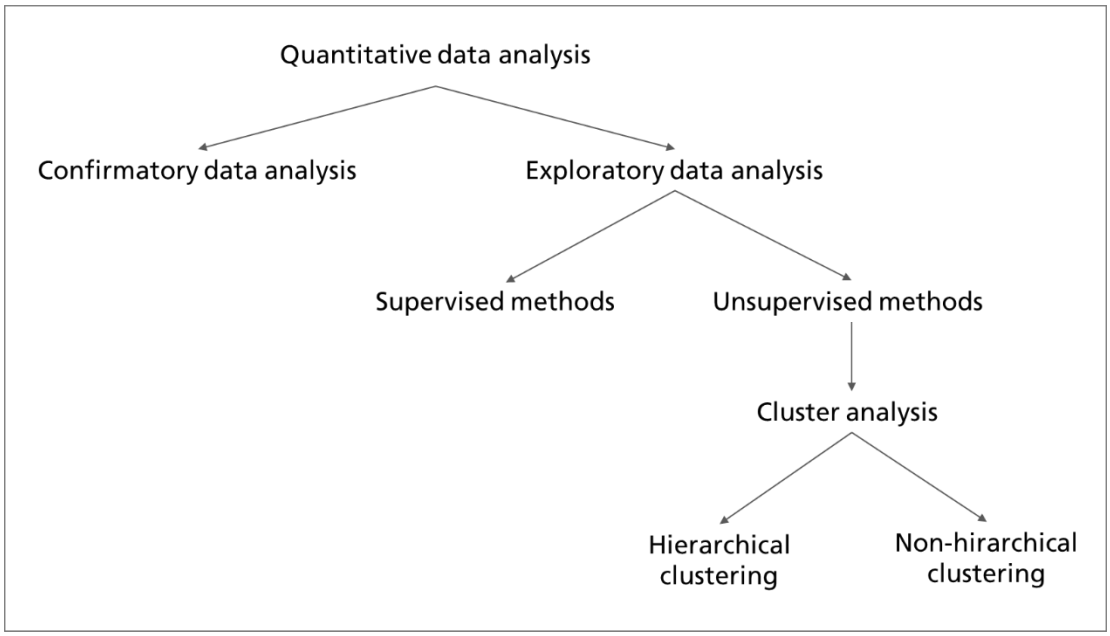
In the following, the method used to analyze the data is chosen and its procedure and steps are defined.

5.1.2.1. Chosen data analysis method

To summarize, process and analyze data, researchers developed quantitative methods for data analysis (Jain, 2010; Xu & Wunsch, 2005). The Figure 21 presents the rational that lead to the selection of cluster analysis as data analysis method.

Quantitative data analysis can serve two broad research goals: exploration or confirmation (Bryman & Bell, 2015; Creswell, 2009; Tukey, 1977). Confirmatory data analysis serves to validate pre-defined hypotheses (Bryman & Bell, 2015; Creswell, 2009; Tukey, 1977). Exploratory data analysis techniques on the other hand serve to understand general characteristics by structuring data into higher dimensions (Bryman & Bell, 2015; Creswell, 2009; Tukey, 1977). According to Jain (2010, p. 651)*"organizing data into sensible groupings is one of the most fundamental modes of understanding and learning".* While the data are analyzed quantitatively, the results have a qualitative and explorative nature.

Figure 21. Decision tree leading to the choice of data analysis method (Source: Own figure based on Bryman & Bell, 2015; Creswell, 2009; Tukey, 1977, Jain, 2010)



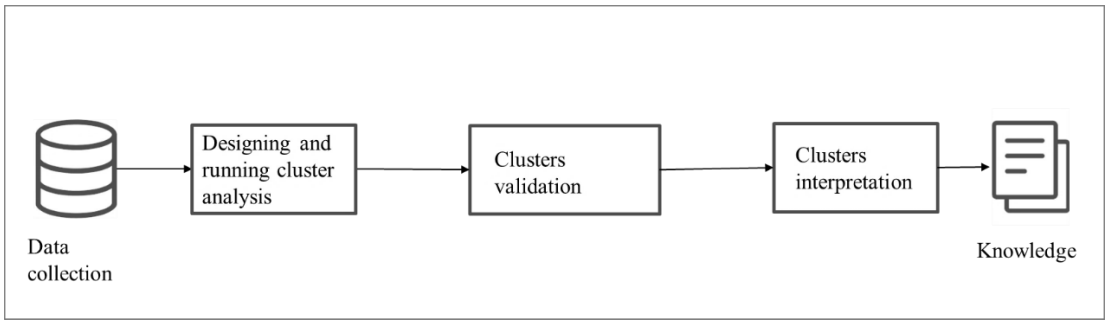
Data can be grouped by either supervised or unsupervised learning methods (Jain, 2010). Supervised learning methods are classification or discriminant analyses which tag objects with prior category labels (Jain, 2010). On the contrary, unsupervised learning methods are multivariate methods that group or cluster objects *"according to measured or perceived intrinsic characteristics"* (Jain, 2010, p. 651). Cluster analysis is one of the most used unsupervised learning methods. Cluster analysis can define higher structures in data to explore or understand a phenomenon (Jain, 2010). Jain (2010, p. 652) provides an operational definition of cluster analysis : *"Given a representation of n objects, find K groups based on a measure of similarity such that the similarities between objects in the same group are high while the similarities between objects in different groups are low".*

Cluster analysis is a relatively recent method in BM research. This method has been used to define types or patterns of BMs in one single industry or across many sectors (Camisón & Villar-López, 2010; Morris et al., 2013; Tangour et al., 2019; Täuscher & Laudien, 2018). For instance, Morris et al. (2013) use cluster analysis to define seven BM designs in the Russian Food Service industry based on secondary data from 289 companies. By comparing the BM designs, they explore the relationship between BM designs and the performance of Russian firms in the food service industry (Morris et al., 2013).

Similarly, Camisón and Villar-López (2010) studied the performance of 159 Spanish companies in 19 different industries by clustering their answers to a survey into four patterns of BMs.

The Figure 22 summarizes the steps followed to conduct the cluster analysis.

Figure 22. Overview of the cluster analysis process (Source: Own figure based on Mazzocchi, 2008; Xu & Wunsch, 2005)



In the following the single steps to design and run the cluster analysis are presented, followed by steps for its validation.

5.1.2.2. Design and run cluster analysis

There are thousands of clustering algorithms that have been proposed by many scientific disciplines, ranging from taxonomists, social scientists, statisticians, computer scientists to biologists and medical researchers (Jain, 2010). Algorithms used for cluster analysis can be distinguished in two broad groups: hierarchical and non- hierarchical clustering algorithms (Jain, 2010; Mazzocchi, 2008).

Hierarchical clustering algorithms can take two directions to form clusters: either agglomerative (bottom-up) or divisive (top-down) (Jurowski & Reich, 2000). Agglomerative and divisive clustering reach the same results: at one are all objects as individual clusters and at the other end they all form a unique cluster (Jurowski & Reich, 2000; Mazzocchi, 2008). Then, the individual clusters are combined in many steps, in smaller clusters according to their (Jurowski & Reich, 2000; Mazzocchi, 2008). On the downside, hierarchical methods are found rigid, because once an object is attributed a cluster, it remains in that cluster during the subsequent steps (Mazzocchi, 2008). Hierarchical clustering algorithms differ in respect to how proximity (similarity) between any two clusters is defined (linkage definition) (Jurowski & Reich, 2000; Mazzocchi, 2008).

The most popular hierarchical clustering algorithms are single-linkage, average-linkage, and complete-linkage methods as well as centroid and Ward methods (Jurowski & Reich, 2000; Mazzocchi, 2008).

Determining the final number of clusters is based on the interpretation of visual representations such as dendrograms (Mazzocchi, 2008). All cluster solutions (at every step of the hierarchical clustering) are nested in the dendrogram (with a nesting distance) (Zhang et al., 2017). By interpreting the dendrogram, researchers can draw a line at a chosen nesting distance to fix the number of appropriate clusters (Mazzocchi, 2008).

Non-hierarchical clustering methods, such as K-means works in successive iteration of the same procedure until an optimum constitution of clusters is achieved (Jain, 2010; Mazzocchi, 2008). First, a fixed number of K-clusters (seeds) representing the first aggregation centers are defined. Second, all objects are assigned to the closest cluster. Third, a new center (new position) of the cluster is calculated based on the objects it contains. Finally, the second and third steps are repeated until no re-clustering of the objects is necessary (convergence is achieved). K-means clustering requires the number of K clusters and initial seeds positions to be defined ahead of the clustering (Mazzocchi, 2008).

In Table 16, Mazzocchi (2008) summarizes the main advantages and disadvantages of hierarchical and non-hierarchical clustering algorithms.

Table 16. Comparison of hierarchical and non-hierarchical methods in cluster analysis (Source: Mazzocchi, 2008)

Hierarchical methods	*Non-hierarchical methods (K-means)*
• No decision about the number of clusters • Problems when data contain a high level of error • Can be very slow, preferable with small data-sets • Initial decisions are more influential (one-step only) • At each steps they require computation of the full proximity matrix	• Faster, more reliable, works with large data-sets • Need to specify the number of clusters • Need to set the initial seeds • Only cluster distances to seeds need to be computed in each iteration

Instead of choosing between the two clustering approaches, Mazzocchi (2008, p. 270) suggests a new procedure that combines hierarchical and non-hierarchical clustering methods.

This procedure uses *"a hierarchical method for a statistically-based definition of the number of clusters and a non-hierarchical method (the k-means method) for the actual clustering"* (Mazzocchi, 2008, p. 270). This procedure mitigates the rigidity associated with the hierarchical clustering as well as the arbitrage associated with fixing the number of clusters in K-means method (Mazzocchi, 2008).

In the procedure proposed by Mazzocchi (2008) a statistically based method is sued to define final number of clusters, the issue of defining the clustering variables remain unsolved. According to the coding framework (see Table 15), each object in the dataset is defined according to 22 variables. Virtually, any one of these variables can be selected to conduct the clustering. Choosing the clustering variables can be the most subjective step of cluster analysis. Often this choice can be based on the research question, on the theory or on other arguments that researchers can define. Depending on the choice of the variables the outputs of the clustering can vary dramatically.

As described above the most popular hierarchical clustering algorithms (e.g., average-linkage, centroid, or Ward methods) require a relatively subjective visual interpretation of the dendrogram to define an optimal number of clusters. Additionally, these algorithms require the inputs of chosen clustering variables. For both these reasons a different hierarchical clustering method has been selected that is called "two-step cluster analysis". This method is a hybrid hierarchical clustering method found in the statistical software IBM® SPSS® (Mazzocchi, 2008). The two-step cluster analysis determines statically an optimum number of final clusters and provide evidence on the most influential variables (Mazzocchi, 2008). This hierarchical clustering algorithm is conducted according to so-called information criteria (Mazzocchi, 2008). The Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) are the most used information criteria (Mazzocchi, 2008).

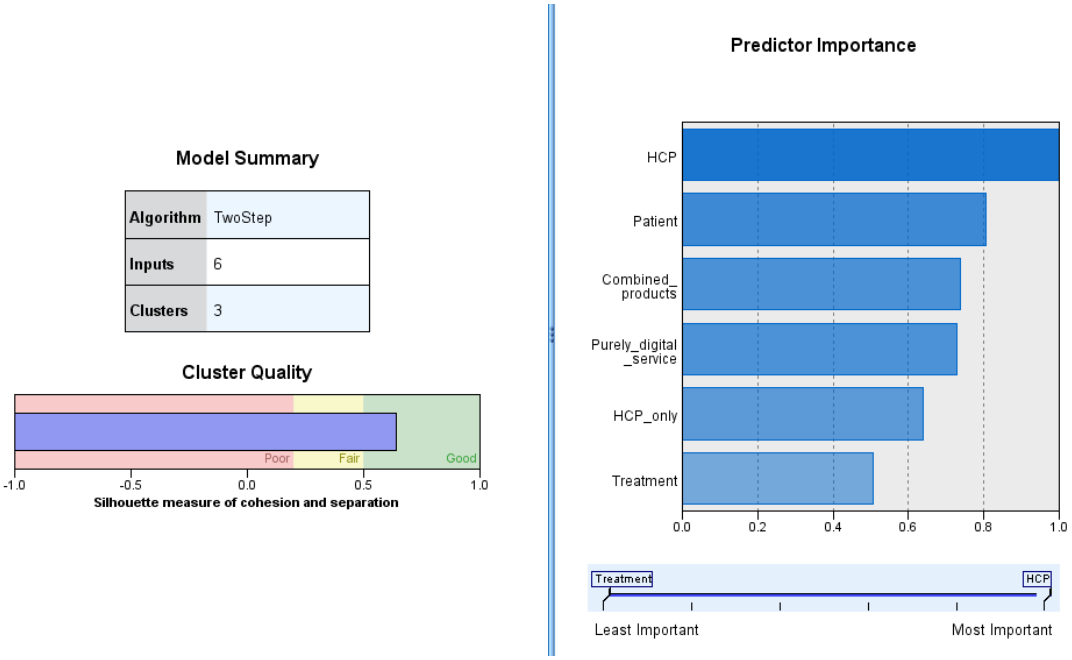
First, the outputs of the two-step cluster analysis provide visual representation of the clustering quality that is segmented in poor, fair and good. The visual representation of the clustering quality is made according to the silhouette measure of within clusters coherence and between-clusters separation (IBM Docs, 2021). The visual representation of the clustering quality enables researchers to amend the clustering setting, to produce better clustering quality (IBM Docs, 2021).

The amendment concerns the choice of variables included in the clustering. SPSS shows the degree of influence of the selected variables on the quality of the clustering based on the function called: Predictor Importance View. According to IBM Docs (2021), *"the Predictor Importance view shows the relative importance of each field in estimating the model"*. Field are the variables selected to conduct the clustering. By variating the choice of variables used during SPSS's two-step cluster analysis, the variables that are most important can emerge.

The optimum number of final clusters is found by iterating the two-step cluster analysis until a good quality of clustering is reached. In each iteration less influential variables are excluded. As shown in Figure 23, the optimal number of clusters is three and a good cluster quality is reached by selecting the following variables:

- V1- Purely digital service
- V2- Combines products
- V6- Treatment
- V11- Patient
- V13- Healthcare professional (HCP)
- V16- Healthcare professional (HCP) only

Figure 23. Cluster quality and predictor or importance from SPSS's two-step cluster analysis (Source: Own figure)



The identified variables and the optimal number of final clusters are inputted in the K-means algorithm to derivate the final clusters.

The statistical software IBM® SPSS® is chosen to perform the clustering since it does not require any coding skills (like R and SAS) and offers the two-step cluster analysis (IBM Docs, 2021). The method and results of the validation of the K-means clustering are presented in the following.

5.1.3. Validation of cluster analysis

The validation of the final clusters evaluates the variability within a cluster as well as between the different clusters (Mazzocchi, 2008). A good cluster analysis minimizes the intra-cluster variability and maximizes the inter-cluster variability (Mazzocchi, 2008). It is recommended that the validation of the K-means method is based on outputs of the clustering method (Mazzocchi, 2008).

The iteration history and one-way ANOVA test are used to evaluate and validate outputs of the clustering method. The iteration history records all iterations of the clustering until convergence (no more re-clustering of the objects) is achieved (IBM Docs, 2021). Table 17 shows that all three clusters are stable as of the 3rd iteration (Change in clusters centers equal 0). Most objects are attributed very fast to their final clusters. The one-way ANOVA test shows that sum of squares between cluster is significantly different from those within clusters (see Table 18). The quality of clusters is sufficient, and the clustering method is validated

Table 17. Iteration History of the K-mean cluster analysis (Source: Own table)

	Change in Cluster Centers		
Iteration	**1**	**2**	**3**
1	0,800	0,700	0,300
2	0,052	0,118	0,103
3	0,000	0,000	0,000

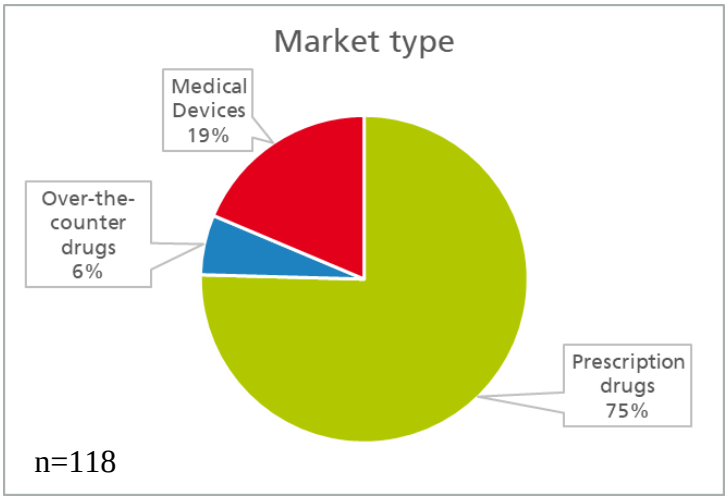
Table 18. Outcomes of the one-way ANOVA test (Source: Own table)

		Sum of Squares	df	Mean Square	F	Sig.
Purely digital service	Between Groups	8.890	2	4.445	28.619	.000
	Within Groups	13.357	86	.155		
	Total	22.247	88			
Combined products	Between Groups	7.364	2	3.682	21.470	.000
	Within Groups	14.748	86	.171		
	Total	22.112	88			
Treatment	Between Groups	2.797	2	1.398	6.204	.003
	Within Groups	19.383	86	.225		
	Total	22.180	88			
Patient	Between Groups	16.354	2	8.177	150.986	.000
	Within Groups	4.657	86	.054		
	Total	21.011	88			
HCP	Between Groups	12.887	2	6.443	108.846	.000
	Within Groups	5.091	86	.059		
	Total	17.978	88			
HCP only	Between Groups	9.289	2	4.645	54.922	.000
	Within Groups	7.273	86	.085		
	Total	16.562	88			

5.2. Results: Digital healthcare packages proposed by Big Pharma firms

In total, 118 digital products and services have been identified, from which 95 are attributed to traditional Big Pharma firms and 23 to recent Big Pharma firms. Figure 24 shows that the digital products and services offered by Big Pharma firms target primarily the prescription drug market (75%), then the medical devices market (19%) and finally the OTC drugs market (6%).

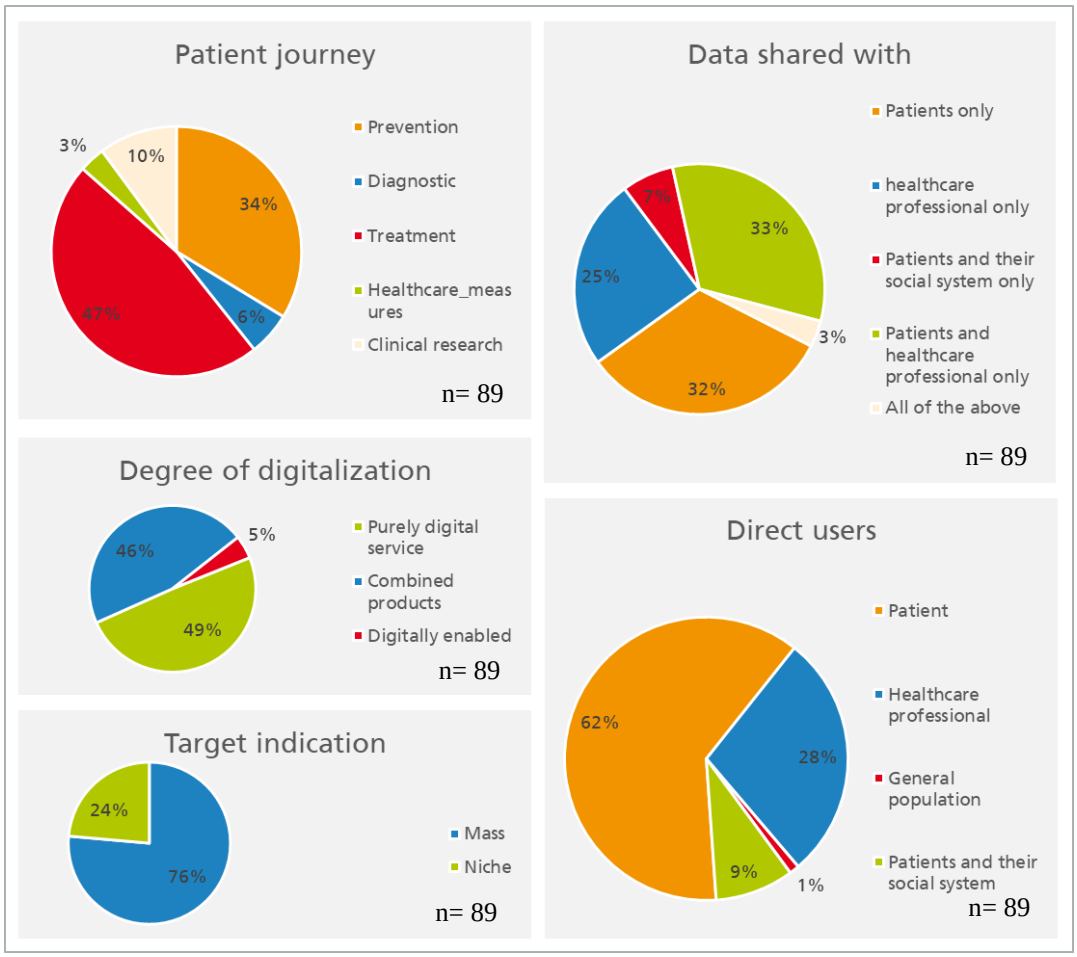
Figure 24. Distribution of digital offers of Big Pharma firms according to their targeted markets (Source: Own figure)



Big Pharma firms offer 89 digital offers in the prescription drug market, from which 67 are offered by traditional Big Pharma companies and 22 are offered by recent Big Pharma firms. On average, each Big Pharma firm offers 4 digital products and services. Digital services and products are probably not systematically bundled with all Big Pharma firms' prescription drugs.

Figure 25 shows that digital offers of big Pharma firms embody different value positions. Most of digital offers are designed to be directly used by patients (62%). Regarding the customer segments, no digital offer targets payers neither as direct users nor as recipient of data.

Figure 25. Distribution of value propositions and customer segments of digital offers of Big Pharma firms (Source: Own figure)



Through cluster analysis, data are systematically structured into a limited number of digitally based value positions serving the prescription drug market. In the following the results of the cluster analysis are presented.

Table 19 presents the final number of objects per cluster with a minimum of 11 objects (cluster 3) and maximum of 56 objects (clusters 1). Having clusters of different sizes does not mean that the clustering is not meaningful but rather that the small clusters are underrepresented in the dataset.

Table 19. Number of objects in each Cluster and their final centers (Source: Own table)

	Cluster number		
Variable	**1**	**2**	**3**
V1- Purely digital service	0	1	0
V2- Combined products	1	0	0
V6- Treatment	0	1	1
V11- Patient	1	0	1
V13- Healthcare professional (HCP)	1	0	1
V16- Healthcare professional (HCP) only	0	1	1
Number of objects in each Cluster	**56**	**22**	**11**

In the following, each cluster is interpreted into different digital healthcare packages (value delivery: value position + customer segments and relationships) that are offered by Big Pharma firms.

5.2.1. Value delivery 1: Digital patient support programs

The cluster 1 corresponds to a distinct value delivery of offering digital support programs to patients. With the digital patients support programs (PSPs), Big Pharma firms provide patients, and their support systems with support in all the phases of their diseases, from prevention, diagnostic, treatments, and disease management.

In this package, 60% of the digital offers are a combination of an App with prescribed drugs and 40 % are purely digital services. In the combined digital offers, the App is designed to improve the effect of treatments (e.g., by improving patients' adherence to their prescribed drugs). For instance, patients taking certain drugs of AstraZeneca (e.g., Imfinzi, Lynparza, Brilinta, Tagrisso and Iressa) can be enrolled by their physicians in tailored digital patient support programs. In this example, AstraZeneca rewards patients who take their drugs as prescribed with free goods. All transactions related to this patient support program are conducted on the AZCare Patient App (including uploading proofs, choosing gifts, and following delivery). Another example is a free App offered by AbbVie (recent Big Pharma firm) launched to support women suffering from endometriosis which are prescribed Orilissa® (elagolix). The Ori for Me App offers tracker to manage treatment goals, one-on-one support from dedicated nurses, and personalized life hacks to better live with the disease.

The purely digital services (40%) in this package focus rather on disease management and prevention of side effects and complications. This is, the case of the Therapy Companion Ovarian Cancer App, developed by the German Ovarian Cancer Foundation, AstraZeneca and Merck & Co. Thea App is digital platform containing verified and reliable scientific knowledge to guide and support patients treated with ovarian cancer and their support systems (e.g., relatives).

The 56 objects in this clusters share the common feature that patients (alone 95%; or with their support system 5%) are the sole users of these digital offers. In half of the cases, the information and/or data generated in these digital services are shared only with users. In the remaining cases, patients' data are shared with their HCPs only (39%), their support system only (7%) or all of them (4%). Except Abbott, Boehringer Ingelheim and Bristol Myers Squibb, all Big Pharma companies offer between 1 to 9 products in this cluster (see Table 20). Takeda Pharmaceutical (9) is the most active in digital PSPS, closely followed by AstraZeneca (7).

Table 20. Number of digital offers for Big Pharma firms in cluster 1 (Source: Own table)

Big Pharma firm	**Number of offers**
AstraZeneca	**7**
Bayer	1
Eli Lilly & Co	1
GlaxoSmithKline	3
Johnson & Johnson	1
Merck & Co.	1
Merck KGaA	1
Novartis	2
Novo Nordisk	2
Pfizer	**4**
Roche	3
Sanofi	3
Takeda Pharmaceutical	**9**
Teva Pharmaceutical Industries	**4**
Abbvie	3
Allergan plc	3
Amgen	**4**
Biogen Idec	3
Gilead Sciences, Inc.	1
Total	**56**

5.2.2. Value delivery 2: Digital Healthcare Professionals support programs

Clusters 2 and 3 contain digital offers that are meant to be used by healthcare professionals (HCPs). Big Pharma firms provide HCPs (mostly physicians, pharmacists, and nurses) with support programs, services, and tools to support them in their medical activities. While sharing the same users' group, clusters 2 and 3 differ in two aspects: the degree of digitization of the offers and their ranges of services. Cluster 2 regroups all offers that are purely digital, while cluster 3 contains offers that are digitally enabled. Furthermore, digital services in cluster 2 range from educational programs, diagnostic tools, and devices and Apps for clinical research. On the other hand, cluster 3 regroups services focusing on the prevention and treatment of diseases.

5.2.2.1. Cluster 2. Purely digital Healthcare Professionals support programs

Cluster 2 counts 22 offers from nine traditional Big Pharma firms and four recent ones (See Table 21). All services in cluster 2 are purely digital offers.

Table 21. Number of digital offers for Big Pharma firms in cluster 2 (Source: Own table)

Big Pharma firm	Number of products
Boehringer Ingelheim	1
Bristol Myers Squibb	1
Eli Lilly & Co	1
GlaxoSmithKline	1
Merck & Co.	2
Novartis	1
Pfizer	**6**
Roche	1
Sanofi	1
Allergan plc	**2**
Amgen	1
Biogen Idec	**3**
Gilead Sciences, Inc.	1
Total	**22**

One type of digital services relates to the education of HCPs. HCPs such as physicians but also nurses are required to maintain their competence by learning about new and developing areas of their field.

Big Pharma firms developed many purely digital offers (digests of written publications, online programs, and digital tools) to facilitate the access of HCPs to the latest of scientific knowledge in most efficient way. For instance, GSK's PneumoDoc provides pulmonologist or general practitioner with summarized information about all respiratory and lung diseases such as asthma or chronic obstructive pulmonary disease (COPD).

One third of the digital services (29%) concerns the generation of new knowledge through clinical research. For instance, Pfizer is currently conducting clinical research on a Wearable Sensors System to treat Parkinson's disease patients. The system consists of sensors, mobile devices, and artificial intelligence, which provides precise symptom information to better understand individual disease progressions. The Wearable Sensors System allows physicians and clinical researchers to better understand Parkinson's disease and their treatment. This purely digital offer has been developed through a partnership between Pfizer and IBM®.

Finally, a third type of digital services supports physician during the diagnostic of diseases. For instance, Biogen's CogEval is an App design for iPads, which physician use to evaluate cognitive functions of patients suffering from multiple sclerosis. The App provides a validated two-minute test called Processing Speed Test.

5.2.2.2. Clusters 3. Digitally enabled Healthcare Professionals support programs

Cluster 3 counts 11 offers from six traditional Big Pharma firms and one recent one (see Table 22). The digital services require an associated drug or therapy to produce the desired value position (0% purely digital services).

Table 22. Number of digital offers for Big Pharma firms in cluster 3 (Source: Own table)

Big Pharma firm	Number of products
Abbott Laboratories	**3**
AstraZeneca	**2**
Merck KGaA	1
Novartis	1
Novo Nordisk	1
Roche	**2**
Amgen	1
Total	**11**

Most digital offers in cluster 3 are designed to support HCP in treating patients (73%). For instance, Abbott's Infinity™ Deep Brain Stimulation system supports physicians in the treatment of Parkinson's diseases. When using the Infinity™ Deep Brain Stimulation App, physicians can personalize and control the deep brain stimulation therapy they are applying to their patients suffering from Parkinson's disease. The deep brain stimulation therapy consists of electrodes implanted in patient's body that are connected to a pulse generator. The therapy is totally controlled by the App. This digital offer is sold together as bundled offer containing the therapy and the App. While the App is associated to a medical device, the therapy is competing with prescription drugs for the management of Parkinson's disease which is why it was not classified among the medical devices market.

An example for the prevention of side effects of treatment is provided by AstraZeneca with the App imAE Navigator. It provides HCPs with signs and symptoms, incidence, and strategies for the management of immune-mediated adverse side effects.

Less than one third (27%) of data generated by HCPs are shared with their patients. One purpose of these Apps is to support physicians explain the disease to their patients. For instance, Merck KGaA developed in cooperation with Isostopy SL an augmented reality App that shows Erbitux®'s mechanisms of action to kill tumor cells.

In conclusion, with 89 digital products and services (75%), the prescription drug market is clearly the focus of Big Pharma firms for the implementation of digital technologies. Through digital technologies, Big Pharma firms offer more complementary services. The following digital offers of Big Pharma firms in the prescription drug market are found:

- Patient support programs (PSP)
- Healthcare professional (HCP) support programs

The results of this chapter confirm the ones of chapter 4 (see 4.2.3.1.). All Big Pharm firms developed many digital offers for patients and physicians. The range of services of the haptic PSPs which are described in the IBCO, is also found in the digitized PSPs. Digital PSPs offer two advantages to the haptic ones: customization and systematic data flows. Digital PSPs can be personalized to specific needs of patients, their physicians or support systems. Digital PSPs allow continuous data exchanges for back-coupling of patient's experience with drugs' producer.

They can be even described as health focused after-sales services of Big Pharma firms. Digital PSPs show that Big Pharm firms are adopting a patient centric approach.

Furthermore, it is found that the complementary services provided to physician is not limited to providing educational content. Specifically, offers in cluster 3 show a symbiosis between digital and non-digital products and services to support physicians during their daily duties to patients (e.g., digital diagnostics tools and real time disease surveillance). By positioning themselves as partners in research and science, Big Pharma firms can better engage with the customer segments of HCPs, which ultimately have a positive impact on their profits.

In the next chapter, the main findings of this thesis are summarized and discussed. Additionally, contribution of this thesis to academia, the practice and policy makers are crystalized. Finally, limits of this work are highlighted and suggestions for further research topics are made.

6. Discussion and conclusion

Incumbent firms are challenged by the accommodation of potentially disruptive technologies, because this requires a BM innovation (Christensen et al., 2018; Danneels, 2004; Gilbert, 2003, 2006; Guo et al., 2019; Moreau, 2013; Walsh & Kirchhoff, 2000). The burgeoning literature on the accommodation of disruptive technologies provides only limited insights to support managers of established firms devise new BM designs. Since Big Pharma firms succeeded in accommodating potentially disruptive biotechnologies (Birkinshaw et al., 2018; Capo et al., 2014), design elements of their BM innovation can support other firms to successfully accommodate potential disruptive technologies. This thesis explored how Big Pharma firms accommodated biotechnologies in the design of their BM. For the first time in literature, a detailed design of Big Pharma firms' BMs before and after the advent of biotechnologies is provided (respectively FIPCO and IBCO). The FIPCO and IBPCO (see 4.2.2 and 4.2.3) are highly accurate representation of the reality of practice because of the rigor of the methodology adopted. Based on systematic literature review (see chapter 3), two BMs are conceptually derived, which are then empirically validated and further specified through semi-structured expert interviews (see chapter 4) and a cluster analysis (see chapter 5). This research has the following main findings:

- Big Pharma firms are profitable in providing biotechnology-based drugs in niche market (see 4.2.3.1.).
- Big Pharma firms are delivering the value behind their innovative drugs by bundling them with digital offers to patients and by providing support programs to HCPs (see 4.2.3.1 and 5.2.)**.**
- Big pharma firms accommodated biotechnologies by engaging in various equity-based and non-equity-based collaborations with new entrants and competitors (see 3.2.4. and 4.2.4). This enables the creation of a new value network.

Furthermore, a potentially new response strategy of incumbent firms to disruptive innovation emerged from this thesis. The strategy consists in actively disinvesting in sustaining technology to secure resources for the development of the potentially disruptive technology**.** Following a tremendous strategic reorganization, in 2019 Pfizer cleared out their mature chemical drugs, mostly by ceding entire drug portfolios.

This allowed them to free substantial resources to be allocated to new innovative biotechnology-based drugs. This decision was timely for Pfizer since they were fast in producing the COVID vaccine. Similarly, Novartis ceded all its vaccine portfolio to GSK (with building and staff) to focus on gene therapies.

In the following, the new BM design elements, and their role in the accommodation of potentially disruptive technologies are discussed. The contribution of this thesis to the field of accommodation of potentially disruptive technologies is criticized.

6.1. Implications for academia

This research belongs to the *"ongoing [p]rocess of [b]uilding a [t]heory of [d]isruption"* (Christensen, 2006, p. 39; Christensen et al., 2018). It contributes to the theory of disruptive innovation with respect to the accommodation of new potentially disruptive technologies in the design of an existing firms' BM. Three design elements are found in this research, contribute to the accommodation of biotechnologies by Big Pharma firms. These designs are explained in the next sections.

6.1.1. Targeting new niche markets

Research on the accommodation of potentially disruptive technologies emphasis the need to target emerging niche markets (Christensen, 1997; Guo et al., 2019; Walsh & Kirchhoff, 2000). This research confirms that statement by showing that Big Pharma firms created new niche markets for their biotechnology-based drugs. Thanks to biotechnologies, drugs can be designed to treat only one specific sub-population of patients, that are called niche indications. Niche indications count a significantly small numbers of patients. Drugs targeting niche indications define emerging niche markets. Big Pharma firms define a new profit formula around drugs designed for niche indications, making these new niche markets profitable. The revenue formula for mass indications is defined around relatively lower prices for higher volumes of sales, while profits are made from high economies of scale. For niche markets, drugs can be highly priced since the target population is relatively small. This high price is a requirement for the profitability of the development of such a niche drug. Typically firms accommodate disruptive technologies by introducing new products and services in new niche markets (Guo et al., 2019). For instance, Tesla succeeded by occupying a new niche market of highly priced, luxury sport electric cars (Guo et al., 2019).

Seizing new markets which sizes match opportunities' sizes is one of the requirement for a successful accommodation of disruptive innovations (Christensen, 1997).

6.1.2. New value proposition from digitization and servitization

Based on chapters 4 and 5, in the current BM of Big Pharma firms (IBCO) the value proposition is as follow:

- drugs from chemical synthesis,
- drugs from biotechnologies (biologic synthesis),
- mass indications: Disease with high incidence,
- niche indications: Disease with low incidence, and
- bundling drugs with complementary services.

At least, six forms of complementary services have been found in this research:

- Patient support programs (PSPs)
- Digital PSPs
- Public events for raising awareness,
- Healthcare professionals (HCPs) support programs
- Digital HCPs support programs
- Pharmacovigilance activities

Big Pharma firms bundle their innovative drugs with complementary services to create a comprehensive healthcare package and more value for their customers. As duly explained in chapter 4, digital offers of a Big Pharma firm serve at least one of the following strategic goals:

- To differentiate their drugs from competitors' drugs,
- To generate and exchange data between the patient, the physician, and the company,
- To enable patients to better engage with the Big Pharma company, and
- To enable physician to better engage with the Big Pharma company.

Besides the above-mentioned benefits of bundling drugs with complementary services, Big Pharma firms create value from the mining of data generated through their digital offers. Data mining is a critical step toward better healthcare. The continuous monitoring of vital parameters created significantly more value than a yearly checkup. Mobile phone Apps collect more accurate health related data than asking patients.

Furthermore, data mining supports precision in treatment approaches. For instance, Merck & Co. collaborates with a hospital in California to map the whole genome of patients during their treatment procedures against cancerous diseases. They aim to have a data bank on organs and tissues' responses to exposure to specific oncological product. Through the data bank they can establish a correlation between patients' genetic characteristics and their responses to certain drugs or dosages. With such data, physicians can match specific drugs to patients' genetic profiles. Mining data translates into having a healthcare system that is continuously learning.

The bundling of products and digital services in the value position belongs to the scholarly field on the servitization of manufacturing sectors. Servitization is an "*innovation of a manufacturing organisation's capabilities and processes to shift from selling product to selling an integrated product and service offering that delivers value in use*" (Baines et al., 2009, p. 563). By engaging in a process of servitization, the product manufactured becomes a commodity, while the true value lies within the comprehensiveness of the solution provided to customers. According to Grönroos (1990, p. 27) "*a service is an activity or series of activities of more or less intangible nature that normally, not necessarily take place in interactions between the customer and service employees and/or physical resources or goods and/or systems of the service provider, which are provided as solutions customer problems*." Customers prefer to buy solutions to their problems rather than to buy products. Based on the design of the IBCO, many of the new biotechnology-based drugs are not just offered alone, but within comprehensive healthcare packages, including close follow ups, coaching and further (digital) complementary services.

The main barrier to the larger servitization of manufacturing firms is the issue of profitable monetization (Tronvoll et al., 2020). In the case of Big Pharma firms, monetization of services is complicated. The trend of servitization is slowed down by profitability and stock market considerations. Returns on investments, time to market, and markets capitalizations differ for drugs and services. Big Pharma companies make very calculated bets on some drugs in which they invest tremendously to be rewarded with very high profitability. This high profitability of developing drugs drives the stock market value of Big Pharma firms upon which they are very dependent. Overall, profitability from services will be lower than profitability from drugs. Furthermore, services require higher delivery volumes and much shorter lifecycles.

Engaging in a business of servitization is highly risky for the stock market shares of Big Pharma firms. If and how services will ever be directly generating revenues for Big Pharma firms remains an open question.

Further servitization potential for Big Pharma firms' BMs lies rather with gene therapy, than with traditionally manufactured drugs. Gene therapy is a specific type of precision medicine in which genes are modified to cure diseases. For instance, in 2019 Novartis launched a gene therapy to cure spinal muscular atrophy, a fatal rare genetic due to the absence in infant's genome of a gene responsible for the synthesis of an essential protein. When the drug Zolgensma® is administered, the child's cells are modified in way that they become able to produce the missing protein. Zolgensma® is not manufactured in a factory but created in a laboratory using patient's own blood. To leverage the potential behind such potentially disruptive healthcare paradigms, Big Pharma firms need to rethink their whole value chain and devise further BM innovation.

6.1.3. Creating value through a portfolio of collaboration formats

In the traditional FIPCO BM, Big Pharma firms conduct drug discovery and development predominantly alone and in-house. This is working for chemical drugs, because the large-scale random screening approaches at the base of chemical R&D activities require limited and superficial knowledge of fundamental physiological processes (Cockburn, 2004). On the contrary, the discovery and development of biotechnology-based drugs require distinct knowledge fields of biology (Song, 2017). Consequently, another knowledge base than the one Big Pharma firms accumulated throughout the centuries is required for new biotechnology-based drugs (Hopkins et al., 2007). Birkinshaw et al., (2018) Christensen (1997), Cozzolino et al. (2018) and Danneels (2004) consider collaboration formats as new modes of resource acquisition. This research confirms that many, but not all, biotechnology-based drug discoveries and developments are conducted through diverse collaboration formats (see 4.2.4). Cassiman and Veugelers (2006) confirm that an optimum combination of internal R&D and external knowledge acquisition shortens time-to-market. In this research it is shown that Big Pharma firms engage in equity-based and non-equity-based collaborations with many key partners including competitors.

According to the results (especially in 3.2.4. and 4.2.4), Big Pharma firms engage predominantly in equity-based transactions with new entrants.

From a theoretical perspective, the high rates of equity-based collaborations of Big Pharma firms can be explained by taking a transaction costs theory perspective or through a strategic perspective such as the resource-based theory of the firm (Hagedoorn et al., 2000; Martínez-Noya & Narula, 2018). From one side, transaction costs explain why many Big Pharma firms rather decide to buy innovation than to make it in-house. *'Buying'* new knowledge has lower transaction costs than '*making*' it from scratch and it protects from opportunistic market behavior (Hagedoorn, 2002). According to Downs and Velamuri (2016, p. 41)*"an equity link can serve as a trust substitute"* for Big Pharma firms collaborations with DBFs. Acquisition of small DBFs is a cheap way to fill Big Pharma firms' drying up pipelines (Boni, 2012; Gottinger & Umali, 2008; Greiner & Ang, 2012; van der Gronde et al., 2017).

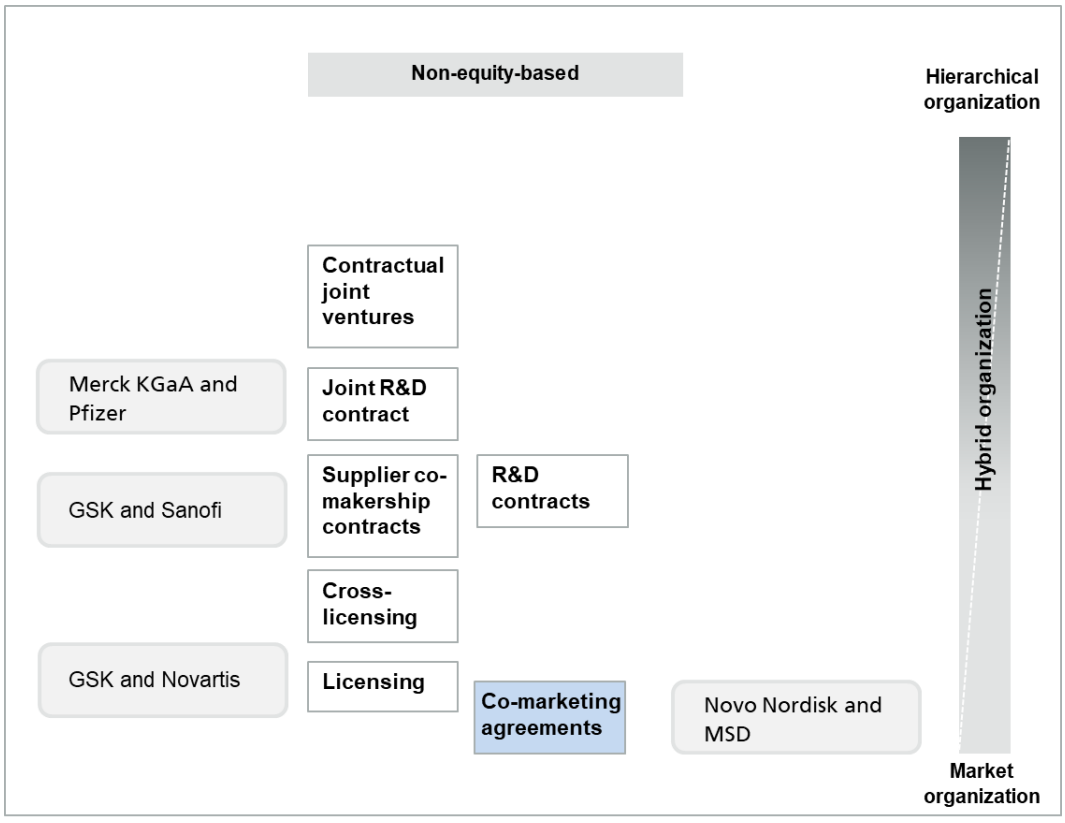
Strategic management perspectives, such as resource dependence theory, provide a value-driven (rather than cost-driven) lens to uncover other motivation to engage in collaborations (Martínez-Noya & Narula, 2018). Firms' motivation to engage in R&D collaborations are the result of *"value-enhancing consideration such as market growth or inter-firm learning through alliances"*, which gain importance with the emerge of technologies such as biotechnologies (Martínez-Noya & Narula, 2018, p. 199). To remain competitive, Big Pharma firms are forced to produce innovative drugs at a faster rate. R&D collaborations are not seen as a desirable option, but as a strategic need (Cassiman & Veugelers, 2006). From the strategic perspective, Big Pharma firms identified DBFs as key partners to gain access to new capabilities related to biotechnologies and design a win-win collaboration with them. DBFs use public financial vehicles available to academic-private partnerships to secure the risky investments of the early stage of drug discovery (Boni & Moehle, 2014). Big Pharma firms have means of scaling up and industrializing R&D activities by leveraging economies of scale and scope of substantial investments in biotechnologies platforms (e.g., genomics) that small and medium sized DBFs do not have (Hopkins et al., 2007). According to Birkinshaw et al. (2018, p. 84) *„[a]cquiring early movers in an emerging technology is a fast way to build sales and capability, and to take out competitors".*

Not all researchers agree on the superiority of equity-based collaboration for gaining access to potentially disruptive technologies. Anand et al. (2010) showed through their quantitative study that technologically disadvantaged firms, such a Big Pharma firms, caught up with emerging technologies better through non-equity-based collaborations with start-ups than with mergers and acquisitions.

Acquisitions present the disadvantages of requiring considerable financial resources and can lead to accumulation of unwanted assets (Anand et al., 2010). Consequently, non-equity-based alliances of Big Pharma firms with start-up DBFs allow them to access new technologies otherwise beyond their reach, and to avoid disadvantages of mergers and acquisitions (Anand et al., 2010). Early stage non-equity-based alliances are favored since they are consistent with the paradigm of ensuring a viable research pipeline (Downs & Velamuri, 2016). A second less frequent type of equity-based collaboration is found in the mergers of competing Big Pharma firms. Through mergers, two companies are combined around a shared strategic and business objective (Demirbag et al., 2007). Mergers between firms in an industry provide *"synergistic coopetition and mutual protection"* (Rebière & Mavoori, 2016, p. 343).

A fundamental contribution of this research concerns the many non-equity-based collaborations between competing big Pharma firms that have been uncovered. As shown in Figure 26, Big Pharma firms concluded joint R&D contracts, suppliers co-makership contracts, co-marketing agreements and licensing agreements, even of whole drug portfolios.

Figure 26. Formats of coopetition between Big Pharma firms with examples (Source: Own figure)



A collaboration between competing companies in the context of global competition is called coopetition and is defined as "*the simultaneous competition and cooperation between two or more rivals competing in global markets*" (Luo, 2007, p. 130). The mix of cooperative and competitive elements (coopetition) between local firms will not remain constant over time (Luo, 2007).

Cooperation among the industry participants increases the interdependencies between them (Song, 2017), which contributes to the creation of a new value network (Guo et al., 2019). A value network is defined as the *"profitability of upstream, downstream and all other collaborative firms associated with the innovation"* (Guo et al., 2019, p. 254). Among the new element of the biopharmaceutical value network, new suppliers of specialized knowledge, equipment, and raw materials are found (e.g., DBFs and CROs). Most of the DBFs assumed the role of specialist supplier of leading-edge new drug candidates to bigger companies (Cockburn, 2004). Many drug candidates are sourced from DBFs, after pre-clinical or first clinical trials phases (Nicol et al., 2013). Certain biotechnology firms adopt a model of pure licensing by poling patents and become one-stop technology platforms shop (Downs & Velamuri, 2016). NOXXON, a DBF based in Germany, counts Pfizer and Hoffmann-La Roche among its partners for licensing and drug discovery of multiple targets in inflammation and Eli Lilly and Co. for licensing and discovery collaboration in migraine (Pwc, 2009). The profound restructuring experienced by the pharmaceutical industry since the mid-1990s (e.g. Merger of the Big Pharma firms) lead to greater consolidation of the industry (Demirbag et al., 2007).

For potentially disruptive technologies to be accommodated on a large scale, the key partners involved in its value network (e.g. suppliers and retailers) must have profitable BM (Christensen, 1997; Guo et al., 2019; Moreau, 2013). This research shows that the new value network around biotechnologies found that DBF and other key partners have found innovative and profitable BMs. Most of new DBFs developed BMs that were new to the industry such as product BM, platform BM, virtual BM, and hybrid BM (Boni, 2012, 2018, 2019; Capo et al., 2014; Downs & Velamuri, 2016; Greiner & Ang, 2012; Hopkins et al., 2007; Horvath et al., 2019; Konde, 2009; March-Chorda et al., 2009; Nicol et al., 2013; Niosi & McKelvey, 2018; Rogers, 2008; Sabatier et al., 2010; Schmieder & Andrew-Wani, 2014; Segers, 2017). Certain DBFs use a BM referred to as Fully Integrated Development Organization (FIDO).

In this case DBFs only conduct the development part of new drugs while the partner conducts the clinical testing and validation, regulators affairs, distribution and marketing (Boni, 2019). DBFs that designed a Platform BM focused on developing a specific technology platform and generated revenues from licensing or selling the technology (tool, equipment or software), making them service providers for Big Pharma companies (Schmieder & Andrew-Wani, 2014).

6.2. Practical implications

This thesis is the first to provide a highly accurate description of the current BM of Big Pharma firms (IBCO). Mid-sized pharmaceutical companies are the type of pharmaceutical companies that can benefit the most from a detailed blueprint of the IBCO. These companies have revenue ranging from 1 to 10 billion USD (Min et al., 2017). In Europe, there are at least 82 companies that are defined as mid-size pharmaceutical companies (Novasecta Ltd, 2020). Mid-sized pharmaceutical firms share Big Pharma firms' substantial financial resources, global distribution channels and excellence in marketing of innovative drugs (Novasecta Ltd, 2020). The top firms, such as Les Laboratoires Servier or Fresenius, focus on end-to-end development of innovative drugs in limited and specific therapeutic areas (CBR Pharma Insights, L. L.C., 2018). They can learn the most from how Big Pharma firms are succeeding in remaining at the top of their industry and become themselves Big Pharma firms. From the specific results of this thesis, mid-sized pharmaceutical firms get inspirational material for conducting their BM innovations.

"As an applied field, management seeks to develop prescriptive advice for practitioners" (Christensen et al., 2018, p. 1044). Despite the growing number of publications, researchers do not provide managers with sufficient knowledge on BM designs elements to accommodate potentially disruptive innovations. Managers lack explicit knowledge to steer the innovation of their own BMs towards achieving profits from potentially disruptive technologies. This thesis is the first to provide new knowledge on concrete BM design elements for the accommodation of potentially disruptive technologies. It is found that collaboration portfolios and digital servitization are among the successful BM designs to achieve this. Established firms in manufacturing industries should develop complementary digital offers. Furthermore, they should initiate equity-based and non-equity-based collaborations to quickly access potentially disruptive technologies.

For instance, in the automotive industry, original equipment manufacturers could engage in equity-based collaborations with provider of charging stations. Through such collaborations, access to charging stations can be included in the car package. Solving the charging stations issues can increase the sales of electric cars.

6.3. Implications for policy makers

There are two levels of policy makers that can benefit from the outcomes of this research: Healthcare authorities and decision makers developing policies for the promotion of research and innovation.

Thanks to biotechnologies, healthcare is moving towards precision medicine in which the drug is seen as the product compound of a treatment service. The lack of clarity about with whom liability lies in case of an adverse event consequent to the use of personalized treatments remain a big barrier to its accommodation by key stakeholders (e.g., Big Pharma companies and hospitals). New guidelines and regulations play a key role to make a successful transition towards precision medicine. Historically, health authorities, such as the FDA, create regulations and guidelines for pharmaceutical firms that ensures the efficiency, safety, and quality of batches-to-batches production of drugs. In precision medicine, biotechnology-based drugs are not designed to be a one-size-fit-all product manufactured in batches. Like other biotechnology-based drugs, the accommodation of precision medicine could happen by creating win-win collaboration formats between Big Pharma firms and key stakeholders involved in the diagnostics and administration of precision treatments. Consequently, it is recommended that health authorities devise guidelines and regulations that support the creation of new collaboration formats in which many stakeholders can share liability around precision medicine, not just the provider of the precision treatment.

This research provides decision makers who devise policies for the promotion of research and innovation with insights on possible BM designs for the accommodation of potentially disruptive innovation: collaboration portfolios and digital servitization. By understanding innovation dynamics behind these BM designs, as explained in this research, policy makers are supported in devising strategies for the promotion of innovation in their local context.

6.1. Limitations and research outlook

This research is not without limitations. This thesis uses diverse methods of qualitative research (i.e., qualitative content analysis and cluster analysis). While the use of qualitative research methods in this exploratory research was necessary due to the limited amount of literature, it lacks the degree of generalization of results attributed to quantitative research. For instance, cluster analysis, which is a systematic mathematical method, is not immune from requiring subjective inputs (Jurowski & Reich, 2000). Researchers are required to make certain informed decisions (from the practice or theory) such as the attribution of characteristics to objects (Jurowski & Reich, 2000). The method of data collection (i.e., qualitative data analysis of secondary documents) remains subjective to some extent, despite the involvement of three independent researchers to reduce this subjectivity. Future researchers should follow quantitative research methods to empirically test the main finding of this thesis.

Second, the BM perspective cannot explain the accommodation of potentially disruptive technologies in isolation of other perspectives. The BM has proven a valuable perspective to understand established firms' decisions to collaborate to quickly access new potentially disruptive technologies and develop services to capture new needs of new customers (e.g., patients support programs). Whether these BM design elements will lead to firms' success in accommodating potentially disruptive technologies also depends on other perspectives such as the organizational structure in which BM innovations are to be embedded.

Finally, the empirical research in this thesis has focused only on the digital technologies to create complementary services to innovative drugs of Big Pharma firms**.** In fact, digitization is not limited to developing new offers, but has a great role in the internal processes of Big Pharma firms. Artificial intelligence is a digital technological trend that will transform the pharmaceutical industry in the coming years. It will render R&D faster, cheaper, and more ethical. With artificial intelligence, scientists could model structures of proteins and biologic receptors to virtually test the therapeutic and side effects of new drug candidates. Clinical research on humans would not be needed anymore, which would lead to fewer costs for Big Pharma firms.

The following questions remain open: How are Big Pharma firms accommodating this potentially disruptive technologies in their BM? Which type of collaboration formats are they engaging in? What regulatory barriers stand ahead (e.g., the approval of virtual physiological models by the health authorities)? In conclusion, the use of digital technologies in the value creating process of Big Pharma firms is an exciting new direction of research. Such research will contribute to the question of digitization of processes in manufacturing firms in general, not just pharmaceutical ones.

End Notes

[i] Foundation date and headquarter are data found in each Big Pharma firm's website, while their annual revenues or turnovers are obtained from the website: http://www.macrotrends.net/

[ii] Foundation date and headquarter are data found in each Big Pharma firm's website, while their annual revenues or turnovers are obtained from the website: http://www.macrotrends.net/

[iii] The calculation was made using: https://www.in2013dollars.com/us/inflation/1987?amount=1

[iv] Amgen is classified as recent Big Pharma firm and not a DBF in this analysis. For more details, please consult Chapter 2.

The references use the citation style of American Psychological Association: 7th Edition (https://apastyle.apa.org/products/concise-guide)

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Appendix

Appendix 1: Protocol for systematic literature review

Background

I conduct a systematic literature review on BM research in the pharmaceutical industry. The aim is to describe BMs of Big Pharma firms before and after the advent of biotechnologies.

Review questions

- What is the traditional BM of Big Pharma firms?
- What are the changes that occurred in the industry during the biotechnology revolution?
- How do Big Pharma firms create, deliver and capture value out of biotechnology-based prescription drugs?

Search strategy

Data base:

Business/Economics Databases (Databases included: Regional Business News, SPORTDiscus, Business Source Complete, SPORTDiscus with Full Text, EconLit with Full Text, eBook Collection (EBSCOhost))

Search terms:

Business model innovation	Pharmaceutical compan*
AND	
("business model*" OR "business model innovation" OR "innovation in business" OR "business process*" OR "organizational change" OR "strategic change" OR "business framework" OR "revenue model" OR "value creation" OR "value generation" OR "activity system")	("biotechnolog*" OR "red biotechnolog*" OR "pharmaceutical industr*" OR "biopharmaceutical industr*" OR "pharmaceutical compan*" OR "biotechnology firm*" OR "biopharmaceutical firm*" OR "big pharma*" OR "large pharma*" OR "global pharma*")
NOT "except biotechnology"	

Study selection criteria

- Deals with BM concept, as defined in this thesis, in a non-marginal way.
- Deals specifically with pharmaceutical industry in a non-marginal way.

Studies quality criteria

Use EBSCO database quality assessment criteria

Appendix 2: Summary of selected articles from the systematic literature review

Selected papers	FIPCO	Pharma trends	IBCO
Abramawicz, M. (2011)	x	x	x
Adamski, J. et al. (2010) **		x	
Anand, J., et al. (2010)		x	x
Birkinshaw, J., et al. (2018)			x
Boni, A. A. (2012)		x	x
Boni, A. A. (2018)	x	x	x
Boni, A. A. (2019)	x		x
Boni, A. A., Moehle, C. (2014)			x
Branning, G., Vater, M. (2016) **			x
Capo, F., et al. (2014)		x	x
Cockburn, I. M. (2004) *	x	x	x
Debnath, B., et al. (2010) *		x	
Demirbag, M., et al. (2007)			x
Diestre, L., Rajagopalan, N. (2012)	x		
DiMasi, J. A., et al. (1991) *	x		
Downs, J. B., Velamuri, V. (2016)	x	x	x
Gottinger, H.-W., Umali, C. L. (2008) *		x	x
Grabowski, H., et al. (2002) *	x		
Greiner, R., Ang, S. (2012)			x
Hopkins, M. M., et al. (2007)	x	x	x
Horvath, B., et al. (2019)			x
Kohut, M. (2019)	x	x	
Konde, V. (2009)	x	x	x
March-Chorda, I., et al. (2009)			x
Mehraliana, G., et al. (2012) **	x		
Mowery, D. C., et al. (2001) *		x	
Nicol, D., et al. (2013)	x		x
Niosi, J., McKelvey, M. (2018)		x	x
Nuijten, M. (2014)	x	x	x

Selected papers	FIPCO	Pharma trends	IBCO
Rao, S. K. (2010)	x	x	x
Rebière, P., Mavoori, H. (2016)		x	x
Rogers, B. (2008)			x
Sabatier, V., et al. (2010)	x		x
Schmieder, K., Andrew-Wani, C. (2014)		x	x
Segers, J.-P. (2017) *	x		x
Song, C. H. (2017)	x	x	x
Song, C. H., Han, J.-W. (2016) *		x	x
Sorrentino, F., Garraffo, F. (2012)	x	x	x
Tangour, C., et al. (2019) **			x
Tulum, Ö., Lazonick, W. (2018)	x	x	x
van der Gronde, T., et al. (2017) **	x	x	x
Wenzel, M., et al. (2014)		x	x
Wrona, T., Trąpczyński, P. (2012)		x	
Xie, F. (2018) **			x
*DS: Downstream search; **AH: Ad hoc search;			

Appendix 3: Interview guides and accompanying visual aids

Guide for qualitative expert interviews

Hi, thank you for accepting that we talk. Would you like that we talk in French or English?

Do you agree to record the audio of this interview?

Mini Introduction of myself: 5 years IMW, Pharmacist, master in innovation Management, PhD Management.

Would you like to shortly introduce yourself?

This interview is divided in 3 parts

- Part 1, check with you, if the way I summarized who pharmaceutical companies do their business reflects your experience in the practice.
- Part2, I would like to ask you about your experience and knowledge about collaborations for biotech R&D
- Part 3 I have a couple of personal questions, that will only serve to agglomerate and analyze the data

You can ask me questions at any time. (Silence)

Do you see my screen? (Screen sharing to show supporting visuals)

Questions	**Answers/ Instructions**	**Visuals**
Probing questions: *'*Could you say a little more about that?' or 'Are there any other reasons why you think that?'		
To give you a bit a context. **Biotechnologies intended for medical use consists in many technologies that deal with proteins, genes and living organisms and have a great potential to improve the healthcare of many people** in my PhD I defend that the advent of biotechnologies in the 1980s is a breaking point in the industry. I argue that large pharma firms changed the way they conduct business, in other words their business models, to adapt to the new biotechnologies. The goal of my research is to better understand the whys and wherefores of the new BM of Big Pharma. **I define business model as the way a firm creates, delivers and captures value out of a product, which can be goods and/or services.**		
Verify the accuracy of FIPCO and IBCO designs to the practice		
The column on the left represents the business model of big pharmaceutical companies before biotechnology, at the time of the dominance of chemical drugs. Short description! + Big Pharma get free new technology from scientific literature or licensed drug candidates in final clinical phases.	a) Completely accurate b) To some extent accurate c) Not at all accurate. *(Only one answer possible)* (Silence)	**FIPCO / IBCO Tables**

1.1. How do you find the accuracy of FIPCO in relation to the reality of practice?

1.2. What do you find correct and why?

1.3. What do you find incorrect and why?

1.4. What would you add and why?

The column on the right represents the business model of large pharmaceutical companies since biotechnology.
Short description!

a) Completely accurate
b) To some extent accurate
c) Not at all accurate.

1.5. How do you find the accuracy of FIPCO in relation to the reality of practice?

(Only one answer possible)

1.6. What do you find accurate and why?

1.7. What do you find inaccurate and why?

1.8. What would you add and why?

1.9. Why do think the BM of big Pharma firms evolved in that way?

1.10. How to rethink the BM of drugs targeting chronic diseases?

1.11. Do your company still conduct in-house R&D activities? (Refocus on biotech)

a) Yes
b) No

If "b", Jump to question 1.13

1.12. What are these in-house R&D activities?

In this table, I summarize types of partnerships between a big pharma company, and either biotech company, research organization or another Big Pharma. With each partner, different formats of collaboration could be possible.

Table Collab. formats in IBCO

Focus on collaboration formats of Big Pharma firms

1.13. Can you name the partnerships that exist in your organization, if any?

1.14. Have you heard of any of the missing type of partnerships in this table?

a) Yes
b) No

If "b", Jump to question 2.1

1.15. If yes, which one? Could you provide examples?

In the next section, I want to focus on 2 specific types of collaborations. The 1st is licensing agreements between a big pharma and another big pharma. It would be great if you can give me examples you know of.

Prompt 1: definition: **Licensing agreements**
A licensing agreement is non-equity based association (Anand et al., 2010) that allows one party (the licensee) to use and/or earn revenue from the property of the owner (the licensor).Investopedia)

2.1. Have you ever heard of a **licensing** agreement between two Big Pharma companies **to gain access to biotechnologies**?
i.e., biotechnology platform or a biological drug candidate

a) Yes,
b) No, never heard of it.
(Only one answer possible)

If "b", Move to question 2.11.

2.2. Can you describe this partnership?

2.3. Does the partnership concern a technology platform or a new biological drug candidate?

a) Biotech platform
b) New biologic drug

2.4. What would be the benefits of such a partnership?

2.5. What would the risks of such a partnership?

2.6. What is important while selecting the partner Big Pharma?

2.7. How often does this type of partnership happen?

2.8. How long does it take to establish such a partnership?

2.9. What are problems that could arise during/after such a partnership?

2.10. Do you know of another situation?

a) Yes
b) No

If "a" start with question 2.2.
If "b", Move to question 2.11.

Other Collaboration agreements:
Prompt 2: definition: Any non-equity based external relationships (Birkinshaw et al., 2018) except for licensing. It is usually delimited to specific projects such as technology exchanges, testing agreements and research contracts between two or more organizations (Anand et al., 2010).

2.11. Have you ever heard of a **partnership, other than**

a) Yes,
b) No, never heard of it.

	through a license agreement, between two large pharmaceutical companies for access to biotechnologies? i.e., biotechnology platform or a biological drug candidate	*(Only one answer possible)*

If "b", Move to question 3.1.

2.12.	Can you describe this partnership?	
2.13.	Does the partnership concern a technology platform or a new biological drug candidate?	a) Biotech platform b) New biologic drug
2.14.	What would be the benefits of such a partnership?	
2.15.	What would the risks of such a partnership?	
2.16.	What is important while selecting the partner?	
2.17.	How often does this type of partnership happen?	
2.18.	How long does it take to establish such a partnership?	
2.19.	What are problems that could arise during/after such a partnership?	
2.20.	Do you know of another situation?	a) Yes b) No

If "a" start with question 2.11.
If "b", Move to question 3.1.

Questions	**Answers/ Instructions**	**Visuals**
Profiling Questions:		
3.1. Which of the following is your current organization? *(Only one answer possible)*	a) Pharmaceutical firm b) Research organization c) Consultant firm **d)** Others: please specify….	Show card N°1
3.2. How long have you been working in or researching the pharmaceutical industry? *(Only one answer possible)*	a) Less than 5 years b) Between 5 and 10 years c) Between 11 and 20 years d) More than 20 years	Show card N°2
3.3. What geographical reach does your expertise in the	a) National reach b) Bi- or tri-National reach c) Regional reach	Show card N°3

pharmaceutical industry have? *(Only one answer possible)*	d) Global reach e) Others: please specify….	
3.4. With which of the following stakeholders do you interact professionally? *(Many answers possible)*	a) (other) pharmaceutical firms b) Payer, please specify…. c) Patients' organizations d) Physicians or physicians' organizations e) Dedicated Biotechnology firms (DBFs) f) (other) research organizations g) Others: please specify….	Show card N°4
3.5. In which domain do you define your expertise in biotechnologies? *(Many answers possible)*	a) Drug discovery and development b) Drug clinical development (clinical trials) c) Manufacturing and supply d) Regulatory affairs and Market access e) Marketing and Pharmacovigilance f) Nowhere: I never worked with biotechnologies g) Others: please specify…	Show card N°5
3.6. How long have you worked with biotechnologies or biotechnology-based drugs? (Only one answer possible)	a) I work with it since less than 5 years b) I work with it since 5 to 10 years c) I work with it since more than 10 years d) Others: please specify….	Show card N°6

3.7. Is there any other aspect you want to add/ highlight?

3.8. If other examples come to your mind after the interview, could you please send them to me via email, LinkedIn, maybe we can arrange another call?

3.9. Do you think of anyone else I should ask for an interview?

Thank you very much for your support and your time.

Big Pharma's Business Model designs

Fully Integrated Pharmaceutical Company (FIPCO) and Integrated Biopharmaceutical Company (IBCO)

		Before the 1980s: the FIPCO	Since the 1980s: the IBCO
Value delivery	**Value proposition**	Chemical drugs frequently in pills One-size-fit-all value of drugs/ Mass markets	Biologic drugs : - Distinct therapeutic value - Targeted patients sub-groups / **Niche markets**
	Customer segments & relationships	Payers: Automatic reimbursement of drugs Physician: Sampling and detailing model Patients	Payers : **Increased direct relationship** Physicians: Sampling and detailing model Patients: **Towards disintermediation**
Value creation	**Key activities**	In-house drug discovery and development In-house marketing, regulatory affairs Multi-locations manufacturing and global distribution network	In-house / **Collaborative drug discovery and development** activities In-house marketing, regulatory affairs, market access
	Key partners	Not mentioned	**Research organizations, Dedicated Biotechnology Firms (DBFs), other Big Pharma firms**
Value capture	**Revenue streams**	Selling drugs	Selling **highly-priced** drugs Conditional reimbursement schemes
	Cost structure	Drug development (until marketing authorization)	Drug development (until marketing authorization) **Health economics data**

(source: own table)

Fraunhofer IMW

Collaboration option for drug discovery and development in IBCO

	Collaboration partners		
Collaboration formats	**Dedicated Biotechnology Firms (DBFs)**	**Public research organizations**	**other Big Pharma firms**
Licensing agreements	Yes	Yes	Missing
Oher collaboration agreements	Yes	Yes	Missing
Corporate venturing	Yes	Missing	Missing
Mergers	Missing	Missing	Yes
Acquisitions	Yes	Missing	Yes

(source: own table)

Fraunhofer IMW

1. Which of the following is your current organization?
(Only one answer possible)

a) Pharmaceutical firm

b) Research organization

c) Consultant firm

d) Others: please specify….

Fraunhofer IMW

2. How long have you been working in/with the pharmaceutical industry?
(Only one answer possible)

a) Less than 5 years

b) Between 5 and 10 years

c) Between 11 and 20 years

d) More than 20 years

Fraunhofer IMW

3. What geographical reach does your expertise in the pharmaceutical industry have?
(Only one answer possible)

a) National reach (e.g. Tunisia)

b) Bi- or tri- national reach (e.g. Tunisia, Algeria and Morocco)

c) Regional reach (e.g. MENA)

d) Global reach

e) Others: please specify….

Fraunhofer IMW

4. With which of the following stakeholders do you interact professionally?
(Many answers possible)

a) (other) pharmaceutical firms
b) Payer, please specify….
c) Patients organizations
d) Physicians or physicians organizations
e) Dedicated Biotechnology firms (DBFs)
f) (other) research organizations
g) Others: please specify….

Fraunhofer IMW

5. Where do you define your expertise in biotechnologies?
(Only one answer possible)

a) Drug discovery and development
b) Drug clinical development (clinical trials)
c) Manufacturing and supply
d) Regulatory affairs and Market access
e) Marketing and Pharmacovigilance
f) Nowhere: I never worked with biotechnologies
g) Others: please specify…

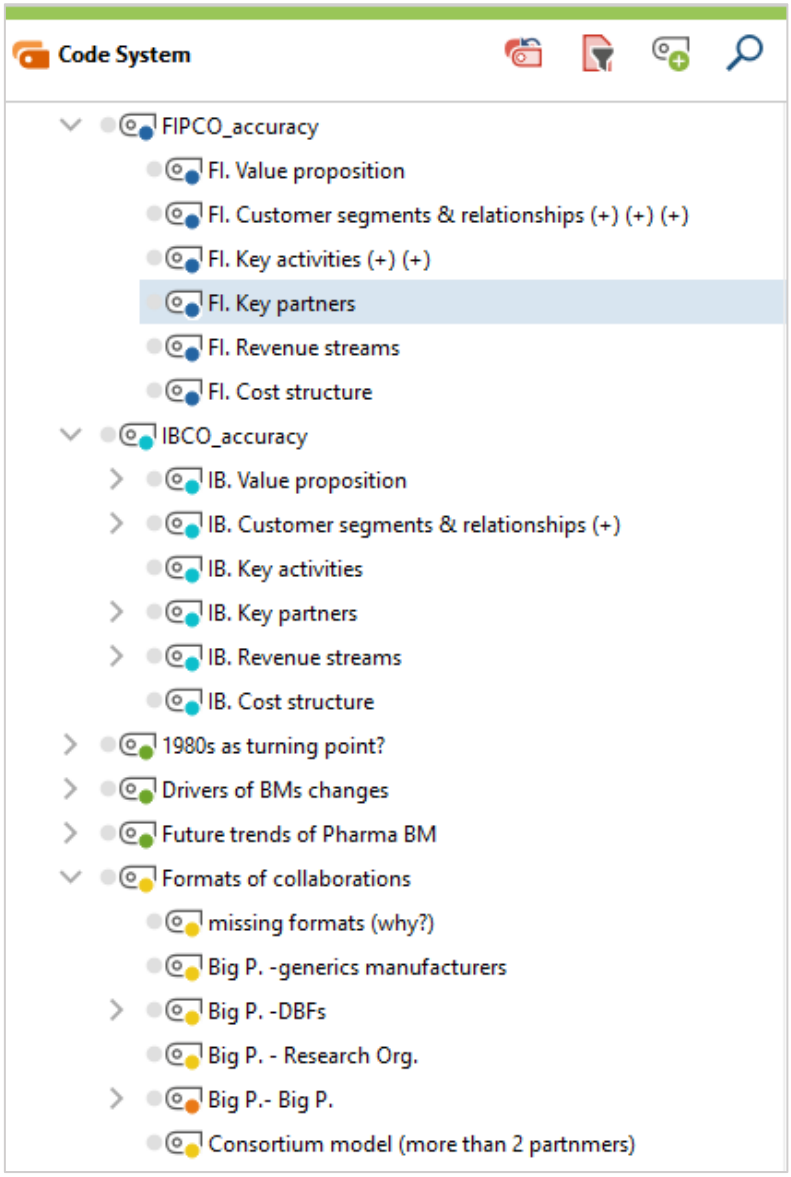
Fraunhofer IMW

6. How long have you worked with biotechnologies or biotechnologies-based drugs?
(Only one answer possible)

a) I work with it since less than 5 years
b) I work with it since 5 to 10 years
c) I work with it since more than 10 years
d) Others: please specify….

Fraunhofer IMW

Appendix 4: Coding system for experts' interviews analysis



Code System	Memo
FIPCO accuracy	Text segments relating to the interviewee's opinion on the accuracy of the entire FIPCO
- FI. Value proposition	Text segments that mention any aspect related to value proposition before the 1980s, any statements that add or confirm or refute that: (At least one of the following) - Only chemical drugs - Frequently formulated in pills - One-size-fit-all value of drugs/ Mass markets
- FI. Customer segments & relationships	Text segments that mention any aspect related to the customer segments before the 1980s, any statements that add or confirm or refute that: (At least one of the following) - There were three types of customers of the pharma companies: the payer, the physician, and the patient - The relationship with the payer was more formal since reimbursement was relatively automatic - The relationship with the physician was based on the sampling and detailing model via medical representatives - There was no particular relationship to the patient
- FI. Key activities	Text segments that mention any aspect related to key activities before the 1980s, any statements that add or confirm or refute that: (At least one of the following) - Companies conducted all their activities in-house. - Key activities consisted in: drug development, drug discovery, marketing, manufacturing, regulatory affairs
- FI. Key partners	Text segments that mention any aspect related to key partners before the 1980s, any statements that add or confirm or refute that Big Pharma firms did not have any key partners
- FI. Revenue streams	Text segments that mention any aspect related to revenue streams before the 1980s, any statements that add or confirm or refute that Big Pharma firms' revenues were from selling drugs
- FI. Costs structure	Text segments that mention any aspect related to costs structure before the 1980s, any statements that add or confirm or refute that Big Pharma firms' costs were from developing, manufacturing, and marketing drugs

Code System	Memo
IBCO accuracy	Text segments relating to the interviewee's opinion on the accuracy of the entire IBCO
- IB. Value proposition	Text segments that mention any aspect related to value proposition since the 1980s, any statements that add or confirm or refute that: (At least one of the following) - Only biologic drugs - Distinct therapeutic value - Targeted patients sub-groups / Niche markets
- IB. Customer segments & relationships	Text segments that mention any aspect related to the customer segments since the 1980s, any statements that add or confirm or refute that: (At least one of the following) - There are three types of customers of the pharma companies: the payer, the physician, and the patient. - The relationship with the payer increased - The relationship with the physician remained based on sampling and detailing model - The relationship with the patient is evolving towards disintermediation
- IB. Key activities	Text segments that mention any aspect related to the key activities since the 1980s, any statements that add or confirm or refute that: (At least one of the following) - Drug discovery and development activities are In-house and through collaborations - In-house marketing, regulatory affairs, market access
- IB. Key partners	Text segments that mention any aspect related to the key partners since the 1980s, any statements that add or confirm or refute that Big Pharma firms'' partner are research organizations, Dedicated Biotechnology Firms (DBFs) and other Big Pharma firms
- IB. Revenue streams	Text segments that mention any aspect related to the key partners since the 1980s, any statements that add or confirm or refute that Big Pharma firms' revenues were from selling highly priced drugs based on conditional reimbursement schemes
- IB. Cost structure	Text segments that confirm or refute that Big Pharma firms' costs were from developing, manufacturing, marketing drugs and for generating health economics data

Code System	Memo
Formats of collaboration	Text segments that mention any aspect related to the advantages, benefits, risks, or process of Big Pharma collaborations
- Missing formats	Text segments that mention any aspect related to reason explain the absence of theoretical collaboration formats from the practice
- Big P. -generics manufacturers	Text segments that mention any aspect related to the collaboration of Big Pharma firms with local generic drugs manufacturers (including examples form the practice)
- Big P. -DBFs	Text segments that mention any aspect related to the collaboration of Big Pharma firms with dedicated biotechnologies firms (including examples form the practice)
- Big P. - Research Org.	Text segments that mention any aspect related to the collaboration of Big Pharma firms with research organizations (including examples form the practice)
- Big P.- Big P.	Text segments that mention any aspect related to the collaboration of Big Pharma firms with other Big Pharma firms (including examples form the practice)
- Consortium model	Text segments that mention any aspect related to the collaboration of Big Pharma firms in the form of a consortium of more than two partners (including examples form the practice)
Is 1980s a turning point?	Text segments that mention any aspect related to interviewees opinion on the choice of 1980s as a turning point and their arguments and examples
Drivers of BMs changes	Text segments that mention any aspect related to divers that lead to the change of Big Pharma firms' BM from the FIPCO to the IBCO
Future trends of pharmaceutical industry	Text segments that mention any aspect related to future trends in the pharmaceutical industry and their possible meaning for or impact on the current and future BM of Big Pharma firms (including examples form the practice)

Appendix 5: Framework for data extraction of digital offers

Codes	Sub-codes	Description	Example
Market type	Prescription drugs	Digital products belong to the market of Medicine that requires a medical prescription to be dispensed	AMI eyecare AR App (Allergan) HUMIRA Complete
	Over-the-counter drugs	Digital products belong to the market of Medicine that one can buy without a prescription	ZeckTag (Pfizer)
	Medical Devices	Digital products belong to the market of devices intended to be used for medical purposes (used for treatment or diagnostic)	TactiCath Quartz™ Contact Force Ablation Catheter
Degree of digitization	Purely digital service	Only digital software and digital hardware (e.g., App)	AZ Respiratory VR (AstraZeneca) Quell® Wearable Pain Relief Technology (GSK)
	Combined products	Bundle of a physical product (e.g., pill), digital hardware (e.g., sensor) and/or digital software	Infinity™ Deep Brain Stimulation (Abbott)
	Digitally enabled	Bundle of physical product (e.g., medical device) and digital software	CardioMEMS™ HF System (Abbott)
Patient journey	Prevention	Any maneuver intended to minimize the incidence or effects of a disease or to assist patients to live with their illness (e.g., diseases management, complication, side effects). Can also be used in combination with a drug/procedure.	HaemTravel (Novo Nordisk) map4health™ (Merck &Co. (MSD) for disease management)
	Diagnostic	Used in combination with a drug/procedure to identify a particular disease, or medical characteristic. Support the healthcare professionals to make informed decision about patients' diagnostic.	OneTouch® (..) OneTouch® reflect
	Treatment	Used in combination with a drug/procedure to fight a disease or disorder; also called therapy (e.g., drugs management). Support the healthcare professionals to make informed	OneTouch Reveal® (Johnson & Johnson)

Codes	Sub-codes	Description	Example
		decision about patient's treatment.	
	Healthcare measures	Support activities for healthy people to remain healthy	Odol-med3 putzzeit (GSK)
	Clinical research	Used in combination with a clinical trial or other steps of clinical research	AURORA Study
Targeted indications	Mass indication	Indicated for a prevalence of the disease or the condition above the limit of 200 000 patients (in USA or Europe) (limit for rare diseases)	Infinity™ Deep Brain Stimulation
	Niche indication	Indicated for a prevalence of the disease or the condition equal or below the limit of 200 000 patients in USA or Europe) (limit for rare diseases)	
Direct users	Patient	A person who is ill and/or is undergoing treatment for disease.	Thea (AstraZeneca) Akne App (GSK)
	Potential Patient / general population	A person might be or not ill and not diagnostic yet or a person with a need to change live hygiene	Quitter's Cicle Odol-med3 putzzeit (GSK)
	HCP	One who treat patients and promote wellness in a clinic environment.	Roche Blood Gas Learn Your ABG
	Patients and their social system	Patients and persons who take care and support directly patient (family and friends, caregivers)	CPP Tracker (AbbVie)
Data shared with	(potential) Patients only	Only the patient can know the data provided by the product	Natrelle 3D (Allergan)
	Health professional only	only Health professional can know the data provided by the product	Calculadora de dosis (Roche)
	(potential) Patients and their social system only	Family and friends can access to data provided by the product	Emotion Space (Pfizer)
	(potential) Patients and health professional only	only the patient and Health professional can know the data provided by the product	myBETAapp™ (Bayer)
	All the above		OneTouch Reveal® (Johnson & Johnson)

Bibliographic description

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Business Model Innovation for Potentially Disruptive Technologies: The Case of Big Pharmaceutical Firms Accommodating Biotechnologies

Leipzig University, dissertation

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Presentation:

Incumbent firms are challenged by the accommodation of potentially disruptive technologies because it requires a business model innovation. The burgeoning literature on disruptive innovation provides only limited recommendations on specific business model elements that can serve to accommodate potentially disruptive technologies. To close this research gap, this thesis explores how big pharmaceutical firms accommodated biotechnologies in the design of their business model innovation to discover successful business model design elements. A qualitative research approach consisting in three studies is adopted. First, following a systematic literature review, 45 papers are selected and qualitatively analyzed. Second, qualitative semi-structured interviews are conducted with 16 experts. Finally, a cluster analysis of all digital offers of big pharmaceutical firms is conducted. This thesis is the first to describe two business model designs of Big Pharma firms from before and since the accommodation of biotechnologies. This research argues that business model designs recommended for the accommodation of potentially disruptive technologies are collaboration portfolios and digital servitization. First, established firms should devise a portfolio of collaboration formats by diversifying breadth of partners (including competitors), and by covering all activities in their value chain. Second, incumbent firms should bundle their products with complementary services, especially those that are digitally enabled. Besides advancing theory on disruptive innovation, the recommended business model design elements can be directly used incumbent firms to commercialize other potentially disruptive technologies. This research supports policy makers in devising strategies for the promotion of the commercialization of potentially disruptive innovations in their specific contexts.

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* ... pp. (total number of pages)

... ref. (number of bibliographical references in bibliography)

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