Towards a more nuanced understanding of the firm-level determinants of radical drug innovations

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Translation of the thesis title into Dutch: Naar een genuanceerder inzicht in de determinanten op bedrijfsniveau van radicale geneesmiddeleninnovaties

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"There was a belief that the failures were due to failed molecules, not a failed approach to the pathway, that these were individual drugs that were often liver-toxic or caused skin rashes because of the specific molecule itself, not the overall approach to the pathway. So there was a lot of conviction from senior management to keep pushing ahead and learn from those mistakes or learn from those failures and eventually we would succeed. And in fact, we did."

(Participant 9 from Study 3)

For the past 20 years I have been working in the pharmaceutical industry for one of the largest pharmaceutical firms in the world. The question of why some pharmaceutical firms bring highly innovative drugs to the market while many others do not has interested me from the beginning, particularly knowing that there are still many diseases to date that cannot be treated effectively, or at all.

The idea to explore this question more systematically, through methodologically sound research, started more than 10 years ago while I was working in the San Francisco Bay Area, the birthplace of biotechnology and home to one of the largest pharmaceutical clusters in the world. While there, I had the chance to work and interact with so many exceptional and inspirational minds in the industry and in academia. When I finally started my PhD journey in Antwerp in 2015, I thought I could finish my research, in addition to my regular job and family commitments, in four years. However, very soon I realized that research in the field of *radical innovation* is a bit like a rabbit hole: vast and fragmented.

So now, six years later and almost at the end of my PhD journey, it is fair to ask – was it worth it? I believe so. The findings of this research add more evidence and clarity about what is important for pharmaceutical firms when they engage in the development of radical drug innovation. At the same time, this research recalls a section from one of Nassim Taleb's books, *The Black Swan: The Impact of the Highly Improbable*, where Taleb discusses the vast private library of Umberto Ecco: It is not so much about what you know (the read books in the library), but the understanding of what you still do not know (the unread books).

The current research would not have been possible without the support, guidance, and patience of my two amazing academic supervisors and co-authors of two published peer-reviewed research papers, Arjen and Bart. I would also like to sincerely thank Dr. Tamara Altman, who helped me get more clarity in my thinking and writing. Also, a special thanks to York Hilger, Dr. Jarek Kriukow, and Gianluca Tarasconi for their valuable support throughout my research journey.

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Summary

Is a *new* pharmaceutical drug per se a better drug? Some research indicates that the answer is not so clear cut. In fact, recent evidence suggests that more than 50 per cent of newly-approved drugs do not offer additional therapeutic benefit when compared to already existing drugs. Thus, in addition to being new, drugs of value to patients and public health also need to be useful, in that they provide some additional therapeutic value (net of treatment risks) when compared with already existing drugs. In order to identify new drugs with additional therapeutic value, a meaningful differentiation beyond mere *newness* is needed. We refer to such novel drugs – those that offer important additional therapeutic value over existing treatment options – as radically innovative drugs or radical drug innovations.

Radical drug innovations have contributed to an important increase in life expectancy globally during the past 100 years. One well-known example of a radically innovative drug is the first antibiotic Penicillin, which was discovered in 1928. Since then, millions of lives have been and are still saved by antibiotics. However, there are currently still many diseases, such as Alzheimer's disease and various types of cancer, that have a high prevalence and an enormous unmet medical need because there are neither disease-modifying nor preventive pharmaceutical drugs available for them, despite massive investments in relevant research and development (R&D) areas. Thus, more radically innovative drugs are needed. However, the rate of radical drug innovation has been declining since the second half of the 20th century, despite increasing investments in pharmaceutical R&D.

Understanding the firm-level determinants involved in successful radical drug innovations is key to increasing this type of output in the future. Research to date has not provided a solid understanding of why so few firms succeed in developing radical drug innovations while many others do not (the majority of radical drug innovations to date have been developed by only a small percentage of all pharmaceutical companies). In addition, research results have not offered any conclusive evidence about which factors are critical for the successful development of radical drug innovations (versus incremental ones). It is known that all drug candidates go through similar R&D processes within a firm, regardless of whether the candidate might turn out to be a radical or incremental innovation, or no innovation at all. It is also known that the R&D process is set up and implemented quite similarly across most pharmaceutical firms. It follows, then, that the organization and execution – at a macro level – of a pharmaceutical firm's R&D process does not seem to be a distinguishing criterion for

radical innovation output. So, a more nuanced understanding of the firm-level determinants of radical drug innovation is needed.

The current research takes up this challenge by focusing on the following four research gaps identified in the current literature on radical drug innovation: (1) definitional ambiguity, (2) unvalidated measures, (3) limited understanding of firm-level determinants, and (4) oversimplified conceptualization of the relationship between some firm-level determinants and radical drug innovation. All four gaps were addressed in this research in the ways described below.

First, in Chapter 2, a definition of radical drug innovation based on novelty and therapeutic impact is introduced. Moreover, empirical evidence of the limitations currently associated with radical drug innovation measurement is provided and discussed. Given the identified limitations with the current measures of radical drug innovation, a new method based on the German health technology assessment (HTA) approach is offered. We argue that this validated measure will enhance our ability to understand radical drug innovation and its firm-level determinants, to compare results across studies, and to stimulate additional research on the topic. Second, in Chapter 3, we present the results from our search of the literature for key firm-level determinants of radical drug innovation. Following a systematic literature review approach, we considered more than 4,100 peer-reviewed journal articles and PhD theses, 38 of which were included in the narrative synthesis. From this review, we offer a conceptual framework of critical determinants of radical drug innovation and highlight managerial and research implications. Third, in Chapter 4, through semi-structured interviews with pharmaceutical R&D experts from the United States, Switzerland, the United Kingdom, and Germany, the current knowledge about firm-level determinants of radical drug innovation, at a more granular level, is further extended. Finally, in Chapter 5, the findings of the entire set of research studies are discussed, and recommendations for future research are provided.

Nederlandse samenvatting

Is een *nieuw* geneesmiddel per definitie een beter geneesmiddel? Sommige onderzoeken wijzen erop dat het antwoord niet zo eenduidig is. Uit recente gegevens blijkt namelijk dat meer dan de helft van de nieuwe goedgekeurde geneesmiddelen geen extra therapeutisch voordeel biedt in vergelijking met bestaande geneesmiddelen. Om relevant te zijn voor patiënten en voor de volksgezondheid moeten geneesmiddelen niet alleen nieuw zijn, maar ook nuttig, in die zin dat ze een zekere therapeutische meerwaarde bieden (na aftrek van de behandelingsrisico's) ten opzichte van bestaande geneesmiddelen. Om te kunnen bepalen of geneesmiddelen een therapeutische meerwaarde hebben, is een zinvol onderscheid nodig dat verder gaat dan louter het *nieuw zijn*. Nieuwe geneesmiddelen die een belangrijke therapeutische meerwaarde bieden ten opzichte van de bestaande behandelingsmogelijkheden noemen we 'radicale (geneesmiddelen) innovaties'.

Die hebben de afgelopen 100 jaar bijgedragen tot een belangrijke stijging van de wereldwijde levensverwachting. Een bekend voorbeeld is het eerste antibioticum, penicilline, dat in 1928 werd ontdekt. Sindsdien zijn – en worden nog steeds – miljoenen levens gered door antibiotica. Er zijn echter nog veel ziekten, zoals alzheimer en verschillende soorten kanker, met een hoge prevalentie en toch een enorme onvervulde medische behoefte. Voor die ziekten is er nog steeds geen preventieve of remmende, laat staan genezende medicatie beschikbaar, ondanks massale investeringen in onderzoek en ontwikkeling (O&O). Er zijn dus meer radicale innovaties nodig. Maar sinds de tweede helft van de 20e eeuw is het tempo van radicale geneesmiddeleninnovatie gedaald, ondanks toenemende investeringen in farmaceutische O&O.

Inzicht in de determinanten op bedrijfsniveau die een rol spelen bij succesvolle radicale innovaties is essentieel om de output in de toekomst te verhogen. Het is tot nog toe niet duidelijk waarom zo weinig bedrijven slagen in radicale innovatie. Het merendeel van de bestaande radicaal innovatieve geneesmiddelen is immers ontwikkeld door slechts een klein percentage van alle farmaceutische bedrijven. Bovendien heeft onderzoek nog geen afdoend bewijs geleverd over welke factoren doorslaggevend zijn voor de succesvolle ontwikkeling van radicale (tegenover incrementele) geneesmiddeleninnovaties. Het is bekend dat alle kandidaat-geneesmiddelen binnen een bedrijf soortgelijke O&O-processen doorlopen, ongeacht of het uiteindelijk om een radicale, incrementele of zelfs geen innovatie blijkt te gaan. Het is ook bekend dat het O&O-proces in de meeste farmaceutische bedrijven op soortgelijke wijze wordt opgezet en uitgevoerd. Hieruit volgt dat de organisatie en uitvoering op macroniveau van het

O&O-proces van een farmaceutisch bedrijf geen onderscheidend criterium lijkt te zijn voor de totstandkoming van radicale innovaties. Er is dus behoefte aan een genuanceerder inzicht in de determinanten op bedrijfsniveau.

In dit onderzoek gaan we de uitdaging aan door ons te richten op vier hiaten die we hebben vastgesteld in de huidige literatuur rond radicale geneesmiddeleninnovatie: (1) ambiguïteit in de definities, (2) niet-gevalideerde maatstaven, (3) beperkt inzicht in de determinanten op bedrijfsniveau, en (4) een al te simplistische conceptualisering van het verband tussen sommige determinanten op bedrijfsniveau en radicale geneesmiddeleninnovatie. Deze vier hiaten werden in dit onderzoek stuk voor stuk benaderd op de hieronder beschreven manieren.

Eerst wordt in hoofdstuk 2 een definitie van radicale geneesmiddeleninnovatie geïntroduceerd op basis van nieuwheid en therapeutische impact. Bovendien wordt empirisch bewijs geleverd van de obstakels bij het in kaart brengen van radicale geneesmiddeleninnovatie. Gelet op de beperkingen van de huidige maatstaven wordt een nieuwe methode voorgesteld, gebaseerd op de Duitse HTA-aanpak (*health technology assessment)*. Wij stellen dat deze gevalideerde maatstaf ons niet alleen meer inzicht kan verschaffen in radicale geneesmiddeleninnovatie en in de determinanten ervan op bedrijfsniveau, maar ook de resultaten van verschillende studies vergelijkbaar maakt, en zo aanvullend onderzoek over dit onderwerp kan stimuleren. Ten tweede presenteren we in hoofdstuk 3 de resultaten van onze zoektocht in de literatuur naar de belangrijkste determinanten op bedrijfsniveau van radicale geneesmiddeleninnovatie. Via een systematische literatuurstudie hebben we meer dan 4100 intercollegiaal getoetste tijdschriftartikelen en doctoraatsverhandelingen in aanmerking genomen, waarvan er uiteindelijk 38 in de narratieve synthese zijn opgenomen. Op basis van dit overzicht bieden we een conceptueel kader van cruciale determinanten van radicale geneesmiddeleninnovatie, met aandacht voor de implicaties op het vlak van bedrijfsvoering en onderzoek. Ten derde wordt in hoofdstuk 4 de huidige kennis over deze determinanten op bedrijfsniveau verder uitgediept door middel van semigestructureerde interviews met farmaceutische O&O-deskundigen uit de Verenigde Staten, Zwitserland, het Verenigd Koninkrijk en Duitsland. Ten slotte worden in hoofdstuk 5 de bevindingen van de volledige reeks onderzoeken besproken, en worden er aanbevelingen voor toekomstig onderzoek gedaan.

Table of contents

List of tables

List of figures

Chapter 1 | Setting the scene

1.1 Introduction

It is well established that radical drug innovations have contributed to an important increase in life expectancy globally during the past 100 years (Kremer 2002; Stiller et al. 2021). One well-known example of a radically innovative drug is the first antibiotic Penicillin, which was discovered in 1928 and first produced industrially in 1942 (Achilladelis 1993). Since then, millions of lives have been and are still saved by antibiotics (Achilladelis 1993; American Chemical Society International Historic Chemical Landmarks 1999).

Given the importance of such innovative drugs for public health, it is important to understand how pharmaceutical firms should manage their innovation processes – which tend to be very lengthy, risky, and costly – so they can successfully develop such drugs. This requires a solid understanding of the critical firm-level determinants involved in the successful development of radical drug innovations. However, the current understanding – and the available evidence to support this understanding – of the relevant firm-level determinants that enable firms to successfully develop radical drug innovations is still rather limited. There are still many diseases, such as Alzheimer's disease, that have a high prevalence and an enormous unmet medical need because there are neither disease-modifying nor preventive pharmaceutical drugs available, despite massive investments in relevant R&D areas (Calcoen et al. 2015; Wolters et al. 2018). Clearly, our current understanding of how to manage the radical drug innovation process is still imperfect, as is evidenced by the low share of radically innovative drugs out of the total number of new drugs (Wieseler et al. 2019), as well as by the concentration of radically innovative drugs coming from a small percentage of pharmaceutical companies (Sorescu et al. 2003).

Before proceeding, we will briefly clarify the terms *innovations*, *radical innovations*, (particularly in the *pharmaceutical industry*; i.e., *radical drug innovations*), and *firm-level determinants*, all of which are central for the current research.

1.1.1 Innovations

Innovations are everywhere. They play an important role in most areas of society, and their influence on the success of national economies, industries, and organizations is well recognized in the literature (Baregheh et al. 2009). However, the meaning of the term *innovation* is not unequivocal because how innovations are conceptualized is dependent on context (e.g., business innovation versus technological innovation versus social innovation), perspective (e.g., who delivers the innovation versus who uses the innovation), and time (e.g., innovation

process models have evolved – over time – from simple and linear to complex and interactive with multiple actors and sources, reflecting changes in our conceptualization of innovation).

Innovation has been explored across a wide range of disciplines and theoretical perspectives. The initial conceptualization of innovation emerged centuries ago, but it only became an important research discipline in the 20th century (Godin 2008), primarily through the work of the economist Joseph Schumpeter in the 1930s and 1940s (Ahuja et al. 2008). Later, in the 1950s and 1960s, other disciplines such as strategy and organizational research started to engage in innovation research. For example, Burr (2014) linked the inception of strategy and organizational research on innovation to tensions between the U.S. and Russia, which led to massive R&D investments in military and aerospace programs in the U.S. Other conceptualizations of innovation (e.g., social innovation) started to emerge at the beginning of the 21st century (Jessop et al. 2013). Depending on the research discipline and theoretical perspective, context-specific definitions of, and measurement approaches for, the concept are used (Kennedy 2009). As such, the literature and research on innovation is highly fragmented. No one theory or discipline can explain all aspects of innovation.

Given the highly fragmented nature of the research on innovation, many researchers have attempted to develop a multi-disciplinary definition of the construct. For example, the 2018 Oslo Manual (i.e., the international reference guide for researching innovation; OECD/Eurostat 2019) defines innovation as a "new or improved product or process (or combination thereof) that differs significantly from the unit's previous products or processes and that has been made available to potential users (product) or brought into use by the unit (process)" (p. 20). This definition of innovation features the newness of a product or service as the central characteristic. Baregheh et al. (2009), based on their literature review of studies from 1934 to 2008, find that innovation definitions – regardless of their theoretical or disciplinary origin – generally highlight *newness* as a key characteristic.

Innovation in a business environment, which is the focus of the current research, is, at its essence, the commercial use of an invention or new idea (Kanter 1983). In this context, innovation can be understood either as an outcome (i.e., a product or service) or as a process that leads to innovation as an outcome (Crossan and Apaydin 2010). Within the business literature, there have been various attempts to conceptualize the typical firm-level innovation process. Innovation process models have evolved from simple and linear to complex, interactive models with multiple actors and sources (Eveleens 2010). Following Stefanovska Ceravolo et al. (2016) and Tidd (2006), there are six key generations of innovation process

models: technology push models (first generation), market pull models (second generation), coupling models (third generation), integrated innovation process models (fourth generation), networked models (fifth generation), and open innovation models (sixth generation).

1.1.2 Radical innovations

When innovations are understood as an outcome, the degree of the newness of an innovation is conceptualized by many researchers dichotomously as either incremental or radical. Incremental innovations, on the one hand, refer to relatively minor changes in existing products, services, or processes that do not tend to result in significant impacts (Tushman and Anderson 1986). Radical innovations, on the other hand, represent products or services that are fundamentally unique and notably impactful. Firms that produce radical innovations (which are also referred to as breakthrough, disruptive, discontinuous, major, or revolutionary innovations; Danneels and Kleinschmidt 2001; Kovacs et al. 2019) tend to experience competitive advantages in the marketplace.

Researchers and managers do not currently agree on a single definition of radical innovation (Green et al. 1995; Kotsemir and Meissner 2013; Kovacs et al. 2019; McDermott and O'Connor 2002). Some, including Forés and Camisón (2016), rely on a one-dimensional definition that focuses on newness (i.e., "fundamental changes in the firm's products, processes, technologies and organizational structure and methods" p. 834). Others conceptualize radical innovations two-dimensionally by considering newness *and* impact. According to this definition, radical innovations refer to products or services that rely on new / unique technology *and* are better able to respond to customer needs when compared to alternative options (e.g., Chandy and Tellis 1998). Findings from Kovacs et al.'s (2019) systematic review of more than 2,000 papers from three decades of radical innovation research confirm the wide variety of radical innovation definitions used in research on the topic.

1.1.3 The pharmaceutical innovation process

Innovation processes – to convert a new idea, knowledge, or technology into a commercial product or service – vary across industries (Pavitt 2005). For example, innovation / product lifecycles in the automotive industry are relatively short, and significant capital investments are needed early on in the process, well before it is clear if a new vehicle can be successfully brought to market (Gerhard et al. 2008). As such, the automotive industry has a strong focus on continuous incremental process innovations, which reduce the time it takes to get to market

as well as manufacturing costs and operational complexities (Gerhard et al. 2008; Vaz et al. 2017).

By comparison, there are a number of notable differences associated with innovation in the pharmaceutical industry (which leads to new drugs). First, the pharmaceutical innovation process tends to be very costly (Aagaard and Gertsen 2011; Dubey and Dubey 2010; Munos 2009; Petrova 2014). According to Guevara et al. (2015), pharmaceutical firms typically invest about 15 per cent of their sales revenues in R&D, which is one of the highest ratios of any global industry. Some estimates indicate that pharmaceutical firms spend up to 1.8 billion U.S. dollars to discover, test, and develop a new drug (Mestre-Ferrandiz et al. 2012). It is important to note that this estimate includes spending on drug candidates that do not make it through the pre-clinical or clinical testing phases. Second, the drug innovation process spans a very long timeline. On average, it takes between 12 to 14 years to get through the rigorous testing needed to bring a new drug to market (Schuhmacher et al. 2016; Sternitzke 2010; Van Norman 2016). As such, R&D investments in this industry tend to be large due to the long R&D cycles. Third, most new pharmaceutical drugs fail during their development (i.e., the industry has typically high attrition rates, which require even more funding). Overall success rates of pharmaceutical R&D programs are very low, with an average of only 5 per cent of drug candidates successfully making it to market (Adams and Brantner 2006; Munos and Chin 2011). Thus, engaging in the drug innovation process is an extremely risky endeavor. Finally, the need for innovation in many other industries (e.g., automotive) is customer-driven, while pharmaceutical drug innovation is primarily science-driven (Aagaard and Gertsen 2011). Indeed, as stated by Gassmann and Reepmeyer (2005): "Few other industries are as driven by science, research and development as the pharmaceutical industry" (p. 233).

1.1.4 Radical drug innovations

Radical *drug* innovations are, like radical innovations in general, conceptualized by varying definitions (de Solà-Morales et al. 2018; Morgan et al. 2008). In fact, a review of 36 academic articles discovered the use of 25 different definitions of drug innovation (de Solà-Morales et al. 2018). Most definitions are one-dimensional (e.g., drug novelty) or two-dimensional (e.g., drug novelty and therapeutic benefit – i.e., impact) and emphasize drug novelty, therapeutic benefits, or unmet medical needs addressed by a drug.

The differentiation of radical from incremental drug innovations is not only of theoretical interest, but also has important practical implications. Policymakers and healthcare

payers in many countries, facing finite resources and increasing healthcare costs, tend to give funding priority to new drugs that address previously unmet medical needs (i.e., radical drug innovations) and deprioritize funding of new drugs that have little to no additional therapeutic value over existing ones (i.e., incremental drug innovations, 'me-too' drugs, or 'follow-on' drugs).

Engaging in the drug innovation process is an extremely risky endeavor; engaging in the drug innovation process for *radical* drug innovations is even more risky because it typically means working on an unvalidated drug target. The drug innovation process tends to be particularly lengthy, risky, and costly. Most drug candidates fail during the drug development process. In addition, very few of those that do make it through the process offer an additional therapeutic benefit over existing drugs. As such, radical drug innovations are rare. When they do happen, they are often enabled by breakthrough advances in science and technology that allow for significant improvement and / or acceleration of the drug discovery and development process (Coccia 2017).

1.1.5 Firm-level determinants of radical drug innovations

Coccia (2017) states that radical drug innovations have "some determinants and patterns that are a *terra incognita* which deserve further scientific analysis to understand" (p. 281). Industry-level incentives to develop radical drug innovations (e.g., intellectual property protection, public funding of basic research, fiscal research incentives for pharmaceutical firms, advanced natural science education and qualification of employees) are quite similar across the major established pharmaceutical R&D clusters (e.g., the U.S., Japan, the UK, Germany, and Switzerland). As such, we argue that they are not the primary reason for the variation in the drug innovation outputs of pharmaceutical firms. Instead, the rather unique pharmaceutical R&D process and how pharmaceutical firms organize it, allocate resources to it, and manage it seem to be more relevant. Consequently, the current research focuses on firm-level determinants of radical drug innovations (instead of industry-level determinants).

Literature reviews have been conducted to identify and classify the firm-level factors that support the successful development of radical innovations generally (e.g., Ahuja and Lampert 2001; Crossan and Apaydin 2010; Slater et al. 2014; van der Panne et al. 2003), though no such research has been carried out to examine innovations within the pharmaceutical industry specifically. In the absence of an industry-specific classification, for the purpose of this introduction, the classification scheme presented by Crossan and Apaydin (2010) is used

as a starting point because it is not linked to any specific industry and has been used frequently in research over the past decade. Crossan and Apaydin (2010) identify three distinct groups of firm-level determinants of innovation: leadership, managerial levers (e.g., culture and organizational structure), and business processes.

It is well recognized that the management of the radical innovations process differs from the management of incremental innovations (Slater et al. 2014), primarily because the product development timelines and the risk of failures are notably higher for radical innovations than they are for incremental innovations (Green et al. 1995). In their extensive literature review, Slater et al. (2014) identify the following firm-level determinants to be particularly important for the development of radical innovations: senior leadership, organizational culture (managerial lever), organizational structure (managerial lever), and the innovation process.

1.2 Research gaps

Radical drug innovations are not only of great importance to public health, but also to pharmaceutical firms that can make considerable profits with new, patent-protected drugs (Arnold and Troyer 2016). Understanding the firm-level determinants that lead to successful radical drug innovations is key to increasing this type of output in the future. However, our current understanding of the firm-level determinants of radical drug innovation is only starting to emerge, as the relevant body of research on this topic is rather small. In their recent bibliometric analysis of pharmaceutical innovation studies, Romasanta et al. (2020) report that only a small number of innovation studies to date examine which firm-level determinants are critical for the successful development of radical drug innovations. In fact, there does not seem to be, to date, any systematic mapping of relevant firm-level determinants of radical drug innovation. As such, it is currently not clear which determinants are more or less critical for the successful development of radical drug innovations. This lack of knowledge is also evidenced by the fact that the majority of radical drug innovations are represented by only a small percentage of pharmaceutical companies (Sorescu et al. 2003). If these determinants were already sufficiently identified and fully understood in the literature and in practice, then we would expect to see greater development of radical drug innovations across the pharmaceutical industry.

In addition, current empirical findings on the topic of radical drug innovation determinants are sometimes contradictory, probably because these studies rely on different

definitions and measures of radical drug innovation. It is well established that the assessment of innovation – in any industry – has unique challenges (Gatignon et al. 2002; Green et al. 1995; Kotsemir and Meissner 2013; Kovacs et al. 2019) because it is a theoretical construct or an "unobservable property of objective reality" (Midgley and Dowling 1978, p. 230). A number of researchers and practitioners have attempted to define and measure drug innovation, primarily with regard to distinguishing radical from incremental drugs. For example, previous research has relied on (1) patent-based measures (e.g., Hohberger 2016; Phene et al. 2006), (2) U.S. FDA New Molecular Entity (NME) designations (e.g., Dunlap et al. 2014; Fernald et al. 2017), and / or (3) priority-reviewed[1] NMEs (e.g., Arnold and Troyer 2016; Dunlap et al. 2016; Kneller 2010; Sorescu et al. 2003; Sternitzke 2010) to identify radical drug innovations. Research that relies on these measures tends to indicate that these measures have been used in previous studies, suggesting that they have been validated. However, none of these three measures of radical drug innovation have actually been validated, which undermines our ability as scholars and practitioners to understand radical drug innovations, explain their antecedents, and demonstrate their implications for management and policymaking.

Finally, although the role of firm-level determinants in the development of radical innovations is complex, research on the topic suggests a somewhat limited understanding of the nuances associated with these factors. For example, many studies associate high R&D spending with radical drug innovations without discussing the nature, timing, and distribution of such expenses (e.g., Arnold and Troyer 2016; Dunlap et al. 2014; Quintana-García and Benavides-Velasco 2011). While findings from these studies indicate that more R&D spending overall is beneficial, we lack detailed information about *how* (e.g., constrained versus unconstrained funding) and *on what* (e.g., how much to invest on the individual sub-processes within the pharmaceutical innovation process) this spending should be allocated. Such information would be helpful in a practical sense, particularly for the early innovation phases (frequently referred to as the fuzzy front-end innovation (FEI) process), during which opportunities are identified and initially assessed (Aagaard 2012; Gassmann and Schweitzer 2014; Hakkarainen and Talonen 2014). It is argued that the FEI process is particularly critical for radical innovations (as opposed to incremental ones; Aagaard 2012, 2015; Rice et al. 2001) because the ideas needed for radical innovations are formulated during the fuzzy front-end phase (Nicholas 2014). Consequently, many believe that the FEI process for radical

[1] Drugs with potentially important therapeutic benefits receive a Priority Review by the U.S. FDA, while all other drugs receive a Standard Review (Sternitzke 2010).

innovations needs to be managed differently than FEI used for incremental innovations (Aagaard and Gertsen 2011; Koen 2004; Reid and De Brentani 2004). However, following Gassmann and Schweizter (2014), "the front end is poorly understood, and managers experience a lack of knowledge on how to best organize the front end" (p. vi).

1.3 Research questions and dissertation outline

The four research gaps that were identified above (i.e., definitional ambiguity, unvalidated measures, limited understanding of firm-level determinants, and an oversimplified / not sufficiently granular conceptualization of the relationship between some firm-level determinants and radical drug innovation) are addressed in this thesis through the following four research questions.

Research question 1: What constitutes radical drug innovations?

Many of the empirical findings in the current literature are contradictory because they rely on different definitions, or no definitions at all, of radical drug innovation, which inhibits our full and accurate understanding of radical drug innovation development. Research question 1 focuses on the key elements of radical drug innovation and attempts to present a more unified definition of the concept. This question is addressed in Chapter 2 (*Do current radical innovation measures actually measure radical drug innovation?*), Chapter 3 (*Determinants of radical drug innovation: A systematic literature review*), and Chapter 4 (*Towards a more in-depth understanding of firm-level determinants of radical drug innovations: Semi-structured expert interviews*). In Chapter 2, an initial definition of radical drug innovation is offered, based on theoretical considerations in the current literature. Chapter 3 presents and discusses the definitions of radical drug innovation used in the 38 papers that are part of the systematic literature review. In Chapter 4, we compile and analyze (practical) definitions of radical drug innovation offered by R&D experts through semi-structured interviews.

Research question 2: Do current measures of radical drug innovation actually assess what they purport to measure?

The problems associated with radical drug innovation measurement are addressed in Chapter 2. We discuss the limitations of the current state of the art in this area and offer a new measurement method based on the German health technology assessment (HTA) approach. Data was obtained for 147 drugs authorized by the European Medicines Agency (EMA) from

2011 to 2016. The innovativeness of these drugs was assessed using current measures of radical drug innovation compared with the newly developed measure.

Research question 3: What firm-level determinants are critical for the development of radically innovative drugs?

To address research question 3, recognizing the nascent nature of this research field, a systematic literature review was conducted to map the current state of the art on this topic. The literature review ultimately considered more than 4,100 peer-reviewed journal articles and PhD theses, 38 of which were included in the narrative synthesis. In Chapter 3, we offer a conceptual framework of critical determinants of radical drug innovation, focusing on three groups of determinants: leadership, managerial levers, and business processes.

Research question 4: How do key firm-level determinants influence the development of radically innovative drugs; particularly with regard to the front-end innovation process?

To appropriately address this research question, a qualitative research approach in the form of semi-structured interviews was chosen for this work, which is included in Chapter 4. Participants for this study are senior R&D experts from various pharmaceutical companies, university research hospitals, and venture capital firms (that invest in pharmaceutical firms) in the U.S. and Europe, which represent two regions with large clusters of pharmaceutical firms that are heavily focused on R&D. The objective of this study is to provide a more nuanced and in-depth understanding of the relationships between firm-level determinants and radical drug innovation.

Chapter 2 | Study 1

Do current radical innovation measures actually measure radical drug innovation?[2]

[2] This chapter has been published as Stiller I, van Witteloostuijn A, Cambré B (2020) Do current radical innovation measures actually measure radical drug innovation? Scientometrics 126:1049–1078

2.1 Abstract

To date, there has been little agreement in the literature on what exactly constitutes radical drug innovation and how to properly measure this important construct. Without a validated measure, our ability to understand radical drug innovations, explain their origins, and demonstrate their implications for management and health policy is limited. This paper addresses the problem of radical drug innovation measurement, provides evidence of the limitations associated with the current state of the art, and offers a new method based on German health technology assessments (HTA). Data was obtained for 147 drugs authorized by the European Medicines Agency from 2011 to 2016. The innovativeness of these drugs was assessed using current measures of radical drug innovation compared with the newly developed measure. Findings indicate that current measures of radical drug innovation are associated with very inconsistent outcomes and do not appear to measure what they purport to measure. This study argues that assessing therapeutic value (as measured by the German HTA) is particularly important, given that drug novelty alone does not conclusively indicate whether a drug will deliver therapeutic value.

2.2 Introduction

A large and growing body of literature focuses on the antecedents, processes, and impacts of radical innovation within a range of environments. More than 170 scholarly papers with the term *radical innovation*[3] in the title were published in the short period from January 2017 to January 2019[4] in journals such as *Research Policy, Journal of Knowledge Management, Academy of Management Proceedings, European Journal of Innovation Management, Journal of Organizational Change,* and *Public Management Review*. This suggests that radical innovations are a central and popular topic across a variety of fields such as organization studies, management science, and public policy (Fagerberg et al. 2005; Gopalakrishnan and Damanpour 1997; Hagedoorn and Cloodt 2003; Jiménez-Jimenez et al. 2008; Sorescu et al. 2003).

Studies on the topic of radical innovation have been carried out without full consideration or rigorous testing with regard to the definition and measurement of this critical

[3]Throughout this paper, the term *radical innovation* is used to describe rare and high-impact innovations, which provide competitive advantages to firms (Tushman and Anderson 1986). Other terms that are synonymous with *radical innovation* are breakthrough, major, and revolutionary innovations (Danneels and Kleinschmidt 2001).
[4]A Google Scholar search on 10 February 2019 resulted in 175 papers with *radical innovation* in the title that had been published since the beginning of 2017.

concept. Indeed, it is challenging to define an innovation's radicalness because it is a theoretical construct, or an "unobservable property of objective reality" (Midgley and Dowling 1978, p. 230). Because radical innovations are abstract and latent, rather than concrete and directly observable, a careful definition and delineation of the construct is required prior to deciding how to measure it. However, the extant literature is replete with a diversity of definitions and, as a result, suffers notably from construct ambiguity. Relatedly, far too little attention has been paid to the development and validation of a standardized measurement of radical innovation. In fact, there is currently no commonly accepted measure of radical innovation (Dahlin and Behrens 2005; Green et al. 1995; Hagedoorn and Cloodt 2003; Verhoeven et al. 2016; Wang and Ahmed 2004).

One large stream of research uses a range of different methods to measure this concept (e.g., surveys and retrospective coding by expert panels). However, many of these methods rely on subjective inputs, which are prone to biases (Sorescu et al. 2003). To combat this problem, innovation scholars have turned to large-scale quantitative assessments in industries such as pharmaceuticals that presumably offer more objective assessments of radical innovations (Sorescu et al. 2003). We focus on the pharmaceutical industry, too, by examining the concept of radical drug innovation, which is very important from the perspective of public health and public health policy.

Research on radical drug innovation has highlighted strong links between radical drug innovation and the success of pharmaceutical firms, as well as the importance of drug innovation within public health policy (Dunlap-Hinkler et al. 2010; Sorescu et al. 2003). Pharmaceutical firms can make considerable profits when they discover, develop, and commercialize new drugs and file patents to protect them (Arnold and Troyer 2016). Radical drug innovations can also improve significant public health issues and address previously unmet medical needs; thus, they are of particular interest to policymakers seeking to improve public health (Arnold and Troyer 2016). A notable example of radical drug innovation is the first antibiotic Penicillin, which was discovered in 1928. Prior to Penicillin, infectious diseases such as pneumonia accounted for high morbidity and mortality worldwide. Policymakers and healthcare payers want to give funding priority to truly innovative drugs that address previously unmet medical needs, and to deprioritize funding of new drugs that have little to no additional therapeutic value over existing ones. Consequently, both pharmaceutical firms and policymakers have an interest in better understanding, developing, and incentivizing radical

drug innovations. However, this requires a clear identification (i.e., definition and measurement) of radical drug innovation.

We conclude that there has been little agreement in the literature to date on what exactly constitutes radical drug innovation and how to measure it appropriately. Many studies use measurement methods that are based on publicly available data. For example, many researchers rely on publicly available drug approval assessment data from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), which regulate the U.S. and European pharmaceutical markets, respectively. Other studies use patent data, which are also publicly accessible through the U.S. and European Patent Offices. Scholars have used these data to measure radical innovations (e.g., through patent counts, patent citation counts, new medical drug counts, and the use of FDA regulatory classifications of newly approved drugs; Sorescu et al. 2003; Verhoeven et al. 2016).

While there have been substantial efforts in prior studies to validate measures of radical inventions, particularly through patent-based measures (e.g., Dahlin and Behrens 2005; Kaplan and Vakili 2015; Verhoeven et al. 2016), there have been limited efforts to explicitly validate specific measures of radical *drug* innovation. As such, it remains unclear what exactly constitutes radical drug innovation, and whether current measures of radical drug innovation actually assess what they purport to measure (de Solà-Morales et al. 2018; Morgan et al. 2008). This undermines our ability to understand radical drug innovations, explain their antecedents, and demonstrate their implications for management and policymaking. Innovation scholars rely on these relatively untested measures to develop and examine their innovation theories. This calls into question the extent to which these developed theories (e.g., regarding the antecedents and outcomes of absorptive capacity[5]) are valid, given that they were tested in pharmaceutical environments with potentially inaccurate measures (e.g., Hohberger 2016; Malva et al. 2015; Phene et al. 2006; Suzuki and Methe 2014; Zucker et al. 2002).

Another challenge associated with these methodological issues is that they inhibit the comparison and integration of results across studies, hence impeding further advances on the topic. For example, while some research on radical drug innovation has concluded that smaller pharmaceutical companies deliver more radical innovations than larger ones (Yamin and Otto 2004), others have come to the opposite conclusion (e.g., Dunlap-Hinkler et al. 2010; Sorescu

[5]Absorptive capacity has been the subject of significant research efforts (Noblet et al. 2011). There is a common understanding in the literature that higher firm-level absorptive capacity leads to better innovation outcomes (Cohen and Levinthal 1990; Lazzeri and Pisano 2014).

et al. 2003). Because each of these studies measured radical drug innovations differently, they do not provide a clear and consistent understanding of the relationship between pharmaceutical firm size and radical drug innovation, as is the case for much research in this area. Indeed, as noted by Bamberger (2017), "after all, no matter how interesting a phenomenon may be, until it can be accurately and reliably measured, our ability as scholars to understand such phenomena, explain their origins and demonstrate their implications for management is extremely limited" (p. 237).

The current paper addresses the problem of radical drug innovation measurement, provides evidence of the limitations associated with the current state of the art, and offers a new measurement method based on the German health technology assessment (HTA) approach. HTA is an evidence-based process that compares the benefits and adverse effects of new drugs versus already existing drugs for the treatment of the same clinical condition (Panteli et al. 2015), thereby enabling physicians and payers to optimize healthcare treatments. These assessments help to ensure that finite public healthcare resources are effectively allocated to truly innovative drugs. Policymakers in an increasing number of countries (e.g., Canada, France, Germany, and the UK) have implemented HTA to determine the additional therapeutic value of new drugs versus existing ones (Ciani et al. 2016; Leverkus and Chuang-Stein 2016). However, HTA methods have not yet been broadly adopted by scholars to measure radical drug innovations in empirical research. The current research develops and validates a new measure of radical drug innovation based on HTA. This validated measure will improve comparability across studies, will help us better understand radical innovation within the industry and its impacts on outcomes, and, in turn, will stimulate further research.

The remainder of this article proceeds as follows. The *Background* section discusses existing definitions and measures of radical innovation in the literature, particularly with regard to innovations within the pharmaceutical industry. The section *Reconceptualization of an existing construct using health technology assessments* introduces our definition and new measurement method for radical drug innovation. The *Data and methodology* section provides details about the study setting, dataset, and methodology. The *Results* section presents the study results, and the *Discussion* section includes a discussion of the results and directions for future work.

2.3 Background

2.3.1 Radical innovation definitions and measurement issues

More than 30 years ago, Dewar and Dutton (1986) pointedly highlighted the ambiguity in the then existing definitions and measures of radical innovation. Today, there is still no general agreement on this topic (Chang et al. 2012; Chiesa et al. 2009; Cruz-Cázares et al. 2013; Dahlin and Behrens 2005; Green et al. 1995; Hagedoorn and Cloodt 2003; Hernandez-Espallardo et al. 2012; Salavou 2004; Verhoeven et al. 2016). Although most of the widely used definitions of radical innovation involve common elements – namely, a break from the past (Dahlin and Behrens 2005; Verhoeven et al. 2016) and an impact on the future, often in the form of competitive advantages in the market (Brem et al. 2016; Cho and Kim 2017; Jiménez-Jimenez et al. 2008; Verhoeven et al. 2016) – this is where the similarities end.

For example, Johannessen et al. (2001) and Colombo et al. (2017) define radical innovation in terms of newness of a commercialized idea or technology. Cantner et al. (2011) consider an innovation to be radical if it is new to the market; but others, such as McDermott and O'Connor (2002), contend that radical innovations require both newness to the market and the firm. Yet others, such as Assink (2006), Chandy and Tellis (1998) and Sorescu et al. (2003), emphasize the importance of value to the customer, in addition to newness. Because the definitions of radical innovation across studies are inconsistent and ambiguous, it is very difficult to consistently operationalize and measure the concept, and to compare findings across studies. For example, Garcia and Calantone (2002) counted 15 different innovation constructs with more than 51 distinct measurement scale items in only 21 empirical studies.

Researchers also vary in their conceptualization and assessment of incremental innovations. The major difference between radical and incremental innovations is the magnitude of novelty and the degree of customer need fulfillment. On the one hand, incremental innovations represent minor improvements, when compared to existing products, services, or processes across both dimensions, offering a marginal extra degree of need fulfillment. On the other hand, radical innovations symbolize major improvements and a large degree of extra need fulfillment in comparion to existing products, services, or processes. It is also important to highlight the important distinction between inventions and innovations because some research is dedicated to radical inventions (e.g., Ahuja and Lampert 2001; Malva et al. 2015), while others analyze radical innovations (e.g., Arnold and Troyer 2016; Dunlap-Hinkler et al. 2010). An invention refers to a new idea or discovery (e.g., which could be patented), whereas an innovation goes beyond the invention, requiring commercial use of the

invention (Kanter 1983). This difference has immediate implications for the radical invention and innovation constructs, as well as their measurement. The present paper focuses on radical *innovations*.

2.3.2 Radical drug innovation definition and measurement issues

Within the literature on pharmaceutical drugs, too, no general agreement exists on the definition of radical drug innovation (de Solà-Morales et al. 2018; Morgan et al. 2008). In their recent literature review, de Solà-Morales et al. (2018) found 25 different definitions of drug innovation in 36 scholarly articles. They discovered, for example, that some definitions rely on drug novelty, while others consider the novelty, therapeutic value, and acceptable costs of the drug. And yet others emphasize unmet medical needs that the new drug addresses. Moreover, many studies that have examined pharmaceutical drug innovations do not even provide definitions for the term. In their systematic literature review on drug innovation, Kesselheim et al. (2013) had to exclude 84 per cent of articles on the topic because they did not contain definitions of drug innovation.

The abundance of radical drug innovation definitions can be explained by the fact that they are context specific (Kennedy 2009). In the specific context of public health, factors in addition to drug novelty are desired because it is now well established from a variety of studies that not all novel drugs are inevitably better when compared to already existing drugs (Aronson et al. 2012; Ciani et al. 2016; Morgan et al. 2008). For example, a recent analysis published in the *British Medical Journal* reports that more than 50 per cent of newly-approved drugs do not offer additional therapeutic benefit when compared to already existing drugs (Wieseler et al. 2019). Thus, in addition to being novel, drugs also need to be useful, in that they provide some additional therapeutic value (net of treatment risks) when compared with already existing drugs. Consequently, drug innovation can be best understood as a two-dimensional construct consisting of drug novelty and therapeutic value. Following Morgan et al. (2008), a radically innovative drug can be characterized as a novel drug that offers important additional therapeutic value over existing treatment options. What exactly characterizes important additional therapeutic value is left open to judgement.

Studies on radical drug innovation are plagued by relatively untested measures of the concept – not surprising, given the lack of definitional consensus. In their literature review, Kesselheim et al. (2013) identified four primary approaches to the measurement of radical drug innovation across 42 studies: drug/New Molecular Entities (NME) counts (21/42, 50%),

therapeutic value (14/42, 33%), patents (4/42, 10%), and economic assessments (3/42, 7%). These different measurement methods have been used to capture radical drug innovation, but there have been limited efforts to validate them, let alone to evaluate their differences and similarities. The following sections include descriptions and limitations of these methods.

2.3.2.1 Drug/NME counts

Some older studies have used the annual number of approved drugs per company as an indication of radical drug innovation, while many recent studies count the number of approved NMEs as a proxy for the concept (Kesselheim et al. 2013). The NME classification is assigned to drugs by the FDA's Center for Drug Evaluation and Research (CDER) after successful review of New Drug Applications (NDA; see, e.g., Fernald et al. 2017; Sternitzke 2010). To designate a chemically synthesized drug as an NME, the FDA requires that the drug contains active substances that have not previously been marketed in the U.S. All other drugs (e.g., drugs that are based on new formulations of previously approved active substances) receive a different (i.e., non-NME) classification by the FDA. As such, NMEs are a measure of drug novelty.

Following the FDA, NMEs can be further differentiated into first-in-class and follow-on drugs (U.S. Food & Drug Administration 2020). A first-in-class drug is defined as a drug that uses – until then – a new and unique mechanism of action for treating a medical condition (Eder et al. 2014; Lexchin 2016). The term *drug class* describes drugs that are grouped together because of their similarities, such as their mechanism of action. The first drug that is based on a new mechanism of action is considered to be a first-in-class drug. However, there is some ambiguity in this approach. For example, a first-in-class drug can be either defined as a drug that uses a new mechanism of action for the first time, independent of any particular disease area, or as a drug that uses a new mechanism of action for a particular disease for the first time, even if the same mode of action was already used for the treatment of other diseases. Because of this ambiguity, researchers frequently examine drug innovation by using the NME method instead of the first-in-class classification, because the NME classification is thought to be unambiguous. Recent studies have categorized NME drugs as radically innovative and non-NME drugs as incrementally innovative (Lexchin 2016).

There are at least two key limitations associated with the approach of measuring radical drug innovation by using the NME classification. First, the NME measure only captures the technological novelty of the drug, but it does not capture the therapeutic value of the drug.

Novel drugs do not inevitably provide additional therapeutic value when compared to already existing drugs, because pharmaceutical companies are not required to demonstrate to the FDA that their drugs have greater therapeutic value than drugs already on the market (Davis and Abraham 2011; Stafford et al. 2009). As such, an NME designation tells nothing about a drug's effectiveness when compared to existing drugs (Davis and Abraham 2011; Jayadev and Stiglitz 2009). As a result, it is not clear whether NMEs are necessarily more valuable than other drugs. Second, the NME characterization is not available for biological drugs, such as recombinant therapeutic proteins, because these go through an approval process that is based on different legislation (Branch and Agranat 2014). Precisely for this reason, biologics are excluded from studies that assess radical drug innovation based on the NME classification (e.g., Cohen and Caner 2016; Dunlap et al. 2013; Sorescu et al. 2003). However, biologics have been a major driver of important clinical progress in areas of high unmet medical need, such as cancer (Collins and Varmus 2015; Schmid and Smith 2005), and need to be included in studies on the topic of radical drug innovation.

2.3.2.2 Patents

Patents are critical for pharmaceutical firms because they provide market exclusivity and, in turn, help to recoup the major R&D investments made in pursuit of new drugs. According to an analysis of the innovative activity of Europe's largest industrial firms, pharmaceutical companies file patents for approximately 80 per cent of their product innovations (Arundel and Kabla 1998). The common use of patents and their data availability in the public domain make them very attractive for empirical research within the pharmaceutical industry. More specifically, counts of both patent forward and patent backward citations[6] are frequently used in the literature to measure radical drug inventions (for a comprehensive overview of patent-based measurement approaches, see Dahlin and Behrens 2005). While forward patent citations are commonly used as a proxy for patent value and impact (Trajtenberg 1990), backward patent citations are understood to be a measure of novelty (Dahlin and Behrens 2005; Shane 2001). Prior studies have identified radical drug inventions based on patents within the top 1% (e.g., Ahuja and Lampert 2001), 2% (e.g., Hohberger 2016; Phene et al. 2006), or 5% (e.g., Singh and Fleming 2010) of the forward citations within the relevant patent class. Although patents are most frequently linked to drug inventions, some researchers have used patent-based

[6]A backward citation refers to a patent that was already available when the patent of interest was granted. A forward citation refers to newer patents that cite the patent of interest that was granted before the newer patents.

indicators to assess radical drug innovations. For example, in their frequently cited paper, Phene et al. (2006) conceptualize radical innovations based on counts of patent citations.

As highlighted by Dahlin and Behrens (2005) and Kuhn et al. (2020), there are important limitations of patent-based measures. First, in their replication of well-known innovation studies, Kuhn et al. (2020) provide "evidence that the use of patent citations is increasingly generating significant measurement error for many academic studies" (p. 112) because of changes in the underlying processes of how patent data are generated. For example, patent citations to not-yet-issued patents (i.e., pending patent applications) have become much more common, but such citations are not captured with current patent-citation methods (Kuhn et al. 2020). Second, patent-based measures have been used to capture important concepts such as novelty, firm market value, and technological impact, but not customer benefit or additional therapeutic value of drugs, which are important in identifying radical drug innovations. Third, patent citation counts are based on the logic that one invention relates to just one patent. However, multiple patents typically protect one pharmaceutical drug (Ouellette 2010). Fourth, there is an important time lag between when a patent is issued and an uptake in citations (Tijssen 2001). Fifth, a risk exists that patents of owners with high status in the industry are cited more frequently (Dahlin and Behrens 2005). Sixth, companies might decide not to file a patent for strategic reasons (e.g., to maintain secrecy; Trajtenberg et al. 1997). Finally, there is an important limitation (in terms of practicality) when collecting patent information for pharmaceutical drugs. It is easy to obtain all patent information for chemically synthesized drugs because the information is publicly available in the FDA's *Orange Book* (U.S. Food & Drug Administration n.d.-a). However, it is not possible to obtain patent information in the same way for biological drugs because the FDA's publicly available *Purple Book* (U.S. Food & Drug Administration n.d.-b) does not contain patent information. As such, to obtain patent information for biological drugs, one either has to search company disclosures and the patent literature for mentions of the biological ingredient and for the tradename (which is extremely time-consuming and potentially error-prone) or purchase access to a commercial database, which is fairly expensive. Although many of the limitations of patent-based measures can be overcome, they reduce the practicality of research because they require context-specific adjustments in the data collection process.

2.3.2.3 Economic assessments

Cost-effectiveness analyses typically measure the benefits of new drugs through quality-adjusted life years (QALYs) compared with alternative drugs or treatment interventions. The main idea is to compare the quality-of-life impact of one drug versus another. QALY analyses are often used to inform health insurance coverage decisions (Weinstein et al. 1996). However, the QALY approach comes with at least two important limitations (Beresniak et al. 2012; Beresniak et al. 2015; de Solà-Morales et al. 2018; Leverkus and Chuang-Stein 2016).

The first limitation is that outcomes of the analysis are reported as change in the length of life, namely adjusted life years. While this might work well with different treatment options for severe diseases such as cancer or heart failure (where the primary outcome is mortality), it is less clear when health outcomes differ widely across diseases or disorders. To better illustrate this point, we refer to the study of Smith and Roberts (2000), who examined the cost-effectiveness of sildenafil – a drug that is used to treat erectile dysfunction. The study, which had the objective to guide healthcare payers on the decision to reimburse the drug or not, concluded that:

> […] the cost-effectiveness ratio [the cost per QALY gained was $11,290 USD; insertion is ours] of sildenafil compared favorably with those of commonly recommended interventions for other medical conditions, costing less than renal dialysis, cholesterol-lowering medication, and coronary artery bypass grafting. (p. 935)

How is such a comparison meaningful? In this case, should payers fund more treatments of erectile dysfunctions instead of renal dialysis? The health outcomes of erectile dysfunctions and renal failures are very different. As such, it is challenging to quantify them with the same measurement system using QALYs.

The second limitation of the QALY approach lies in the methodology for the adjustment of quality of life. There are different methods, such as the time trade-off (TTO) method,[7] for the quality adjustment, and it is well established that they lead to different QALY outcomes (Beresniak et al. 2015). Acknowledging the methodological limitations of the QALY approach, the European Commission funded the ECHOUTCOME research project to examine the validity of the QALY approach. The study, based on more than 1,300 respondents, could not validate the QALY method because there were important differences

[7] The TTO method is based on replies from a sample of people who were asked how many life years they would trade in order to avoid living with a certain health state (e.g., a specific disease or disability).

between the TTO preferences expressed by the respondents and the assumed TTO choices that are part of the QALY calculation (Beresniak et al. 2015).

2.3.2.4 Therapeutic value

Another approach for measuring radical drug innovation is based on the therapeutic value of drugs (Kesselheim et al. 2013). Although there is little consensus on the exact method for assessing therapeutic drug value (Kesselheim et al. 2013), a number of researchers have evaluated therapeutic drug value based on the clinical potential that the FDA assumes at the time of the drug application (e.g., Arnold and Troyer 2016; Dunlap et al. 2016; Kneller 2010; Sorescu et al. 2003; Sternitzke 2010). Drugs deemed by the FDA to have potentially important therapeutic benefits receive an Expedited Review, while all other drugs receive a Standard Review (Chambers et al. 2017; Sternitzke 2010). The FDA has multiple Expedited Review programs: Priority Review, Fast Track, Accelerated Approval, and Breakthrough Therapy. These programs aim to bring potentially innovative drugs faster to patients in need.

Studies of radical drug innovation rely on Priority Reviews, but not the other types of expedited FDA review (i.e., Fast Track, Accelerated Approval, or Breakthrough Therapy), to identify the innovativeness of drugs. This is probably the case because the Priority Review program was established first in 1992, whereas the other FDA Expedited Review programs were established later: the Fast Track program in 1997, and both the Accelerated Approval and Breakthrough Therapy in 2012 (U.S. Food & Drug Administration 2018). Researchers who utilize the therapeutic value approach to radical drug innovation associate the Priority-Reviewed NMEs as radically innovative, and all others as incrementally innovative (e.g., Arnold and Troyer 2016; Dunlap et al. 2016; Kneller 2010; Sorescu et al. 2003; Sternitzke 2010). *Table 1* shows a comprehensive operationalization of drug innovation based on NME and FDA Standard/Priority Reviews.

Table 1 – Operationalization of drug innovation by Sorescu et al. (2003)

	Standard Review	**Priority Review**
Non-NME	Incremental innovation	Market breakthrough
NME	Technological innovation	Radical innovation

While this two-dimensional operationalization of radical drug innovation is conceptually aligned with Chandy and Tellis (1998), who define radical innovation through novelty and customer value, the operationalization of a new drug's therapeutic value through

the FDA Priority Review characterization is potentially flawed. The FDA's Priority Reviews have important limitations, which are the same for the other Expedited Review programs (i.e., Fast Track, Accelerated Approval, and Breakthrough Therapy). First, the FDA uses expedited programs to review drug candidates that are believed (at the time of the submission of the drug application) to offer potentially important clinical improvements. However, there is no guarantee that these drug candidates actually provide therapeutic improvements after they are approved and used (Chary 2016; Darrow et al. 2020; Hwang et al. 2018). Second, recent evidence shows that FDA-expedited programs are, in general, approved on the basis of fewer and smaller clinical trials (Wallach et al. 2018). Drugs approved through Expedited Review programs are more likely to receive FDA safety actions later on (Wallach et al. 2018) because these drugs have higher incidences of safety issues post-approval (Pinnow et al. 2018), including increased incidences of serious adverse reactions (Olson 2008) and safety-related label changes after approval, particularly those representing highest risk warnings (Mostaghim et al. 2017). In summary, while the aim to more quickly bring potentially innovative drugs to patients in need is laudable, shorter review processes based on clinical trials with smaller patient populations lead to greater uncertainty about drug efficacy and safety. There is important evidence that the FDA's Expedited Review programs may lead to the approval of drugs that carry greater risks than benefits. Thus, the use of any of these expedited programs as a single proxy of the additional therapeutic value of a new drug might be problematic.

2.4 Reconceptualization of an existing construct using health technology assessments

As discussed above, there is a wide variety of definitions and measures of radical drug innovation used within research on the topic. It is challenging to measure an innovation's radicalness because it is a theoretical construct. Many of the current measures have not been validated and, based on the discussion in the previous section, may not adequately assess radical drug innovation. The NME characterization and patent-based measures only assess drug novelty. The two-dimensional measure of radical drug innovation NME + Priority Reviews assesses both drug novelty and a drug's therapeutic value, but the operationalization of a new drug's therapeutic value through the FDA Priority Review characterization is potentially flawed.

One solution to address this major limitation may come from utilizing a new, two-dimensional measure that is based on drug novelty, which is captured through the NME classification, and the additional therapeutic value of a drug, measured through Germany's

HTA approach instead of Priority Reviews. The German HTA approach was chosen because it assesses the additional therapeutic value of new drugs based on clinical studies and does not use an approach based upon quality-adjusted life years (QALYs), which has been convincingly judged to be flawed by some researchers (see discussion above and de Solà-Morales et al. 2018; Leverkus and Chuang-Stein 2016).

2.4.1 Health technology assessment

As noted above, when a new drug is approved by regulatory agencies such as the FDA or the EMA, this normally means that the drug is both safe and effective. Regulatory drug approvals are often based on clinical trials that assess the new drug versus placebo treatment (Davis and Abraham 2011; Stafford et al. 2009). Thus, regulatory approval does not necessarily indicate that the new drug is clinically superior to other drugs. Because of this, patients, physicians, and payers have limited ability to compare the benefits of newly approved drugs vis-à-vis already existing ones. This notable gap may drive both suboptimal treatment choices and healthcare resource allocations.

HTA addresses this gap by identifying effective treatment options through the "systematic evaluation of properties, effects, and / or impacts of health technology" (World Health Organization n.d.). HTA is an evidence-based process that examines the consequences of using a healthcare technology (e.g., a new drug or a new treatment procedure) by analyzing its associated medical, social, economic, and ethical issues (Panteli et al. 2015). More specifically, the HTA approach compares the benefits and adverse effects of alternative drugs for the treatment of the same clinical condition (Panteli et al. 2015), thereby enabling physicians and payers to optimize healthcare treatments. HTA may be based on examinations of clinical efficacy, safety, real-world effectiveness, and the social and ethical impacts of using the drug. Many countries (e.g., the UK) require cost-effectiveness assessments to be part of HTA to guide reimbursement and access decisions. The results from HTA are becoming increasingly recognized and considered when making health policy decisions in many countries (Panteli et al. 2015; Postma et al. 2011), including whether a new drug should be reimbursed by public healthcare systems and to predict which patients might benefit most from new drugs.

HTA was implemented in Germany in 2000 (Fricke and Dauben 2009). As part of the German HTA framework, clinical benefits assessments[8] of new drugs were made mandatory in the country in 2011 (Leverkus and Chuang-Stein 2016). This means that all new drugs must be evaluated against a comparator, typically the existing standard of care,[9] to assess the presence and magnitude of the new drug's additional clinical benefits (Schlette and Hess 2013). This assessment first includes an analysis of the pharmaceutical company's dossier by the German Institute for Quality and Efficiency in Healthcare (IQWiG). Subsequently, the Federal Joint Committee (G-BA), which is Germany's highest decision-making body of physicians, hospitals, and health insurance funds, makes final decisions with regard to the drug's added benefits (Schlette and Hess 2013).

The German HTA process results in six possible clinical assessment outcomes: (1) major benefit; (2) considerable benefit; (3) minor benefit; (4) not quantifiable; (5) no additional benefit; and (6) lower benefit (Lauenroth and Stargardt 2017). The IQWiG methodology dictates that a drug with either a sustained or significant improvement of the clinical condition (in comparison to the comparator drug) receive a classification of major or considerable benefit (Leverkus and Chuang-Stein 2016; Skipka et al. 2016). Key factors for a positive assessment outcome are improved overall survival, as well as decreased morbidity and adverse events (versus the comparator drug). Only if an important additional benefit is evident and a positive assessment is obtained can the pharmaceutical company negotiate a premium price with health insurance companies. Otherwise, the price of the new drug is referenced to the price of the comparator drug (Schlette and Hess 2013).

2.4.2 Using NME and HTA to classify radical drug innovations

Before developing a new method to measure radical drug innovation, a careful definition and delineation of the construct is required. In their recent systematic literature review on the definitions of drug innovation, de Solà-Morales et al. (2018) found that drug innovation was most frequently characterized by the therapeutic value of drugs, followed by drug novelty. Building on this characterization, a new drug can be considered radically innovative (1) if it provides evidence for important additional therapeutic value (net of treatment risks) to patients

[8] Benefit assessment of pharmaceuticals in accordance with the German Social Code, Book Five (SGB V), Section 35a.
[9] Guidelines, typically developed by a specialist society, that are generally accepted in the medical community for the treatment of a disease or condition.

when compared to already existing drugs that are intended to treat the same clinical condition and (2) if it is based on a new structure or mechanism of action.

In line with this definition, radical drug innovation can be operationalized through a combination of the NME classification and the German early benefit assessment (part of the HTA approach). As discussed above, the NME classification serves as a measure of a drug's novelty, and the German HTA method is an evidence-based process that assesses the therapeutic value of a new drug. On the one hand, all NMEs that are deemed, through the HTA process, to have a major or considerable additional clinical benefit that can be categorized as radically innovative. On the other hand, drugs with minor benefit, not quantifiable, and no additional benefit classifications can be categorized as incremental or not innovative. This new two-dimensional measure may be more suitable than existing measures because, in addition to considering the newness of a drug, it also assesses the therapeutic value of the drug using transparent and evidence-based methods.

2.5 Data and methodology

2.5.1 Data

Data was collected from a range of public databases of regulatory authorities, government agencies, and institutes. Through manual extraction from the annexes of 2011 to 2016 EMA annual reports (European Medicines Agency n.d.), data was obtained for all 322 drugs that had been authorized for human use by the EMA during that time period. Data included approval year, product name, therapeutic area, and name of marketing authorization holder. After exclusion of nine registrations with the same active substance and indication as well as vaccines, gene therapies (following Alqahtani et al. 2015), and radioactive tracing pharmaceuticals (due to their use in diagnostic imaging), 293 drugs remained. The G-BA database (Gemeinsamer Bundesausschuss n.d.) was then checked to see if an early benefit assessment had been performed for each of these drugs. After drugs without an assessment, primarily due to low sales, were excluded, 163 drugs remained. We then collected patent information for the patented drugs (147 of the 163 drugs have patents). This comprised the final dataset for this study.

For these 147 drugs, additional information was collected from the approved drug product database of the FDA, such as the drugs' NDA classification codes and regulatory review types (priority versus standard; U.S. Food & Drug Administration, n.d.-c), as well as the outcomes of the early benefit assessments from the database of the G-BA. All information

for the patent-based analysis was taken either from the PATSTAT database (European Patent Office n.d.) or a commercial patent database (thinkBiotech LLC n.d.). *Figure 1* summarizes the data collection process. Due to the recent implementation of the German HTA (early benefit assessment) in 2011, the size of the available data set is limited, and no sampling was performed.

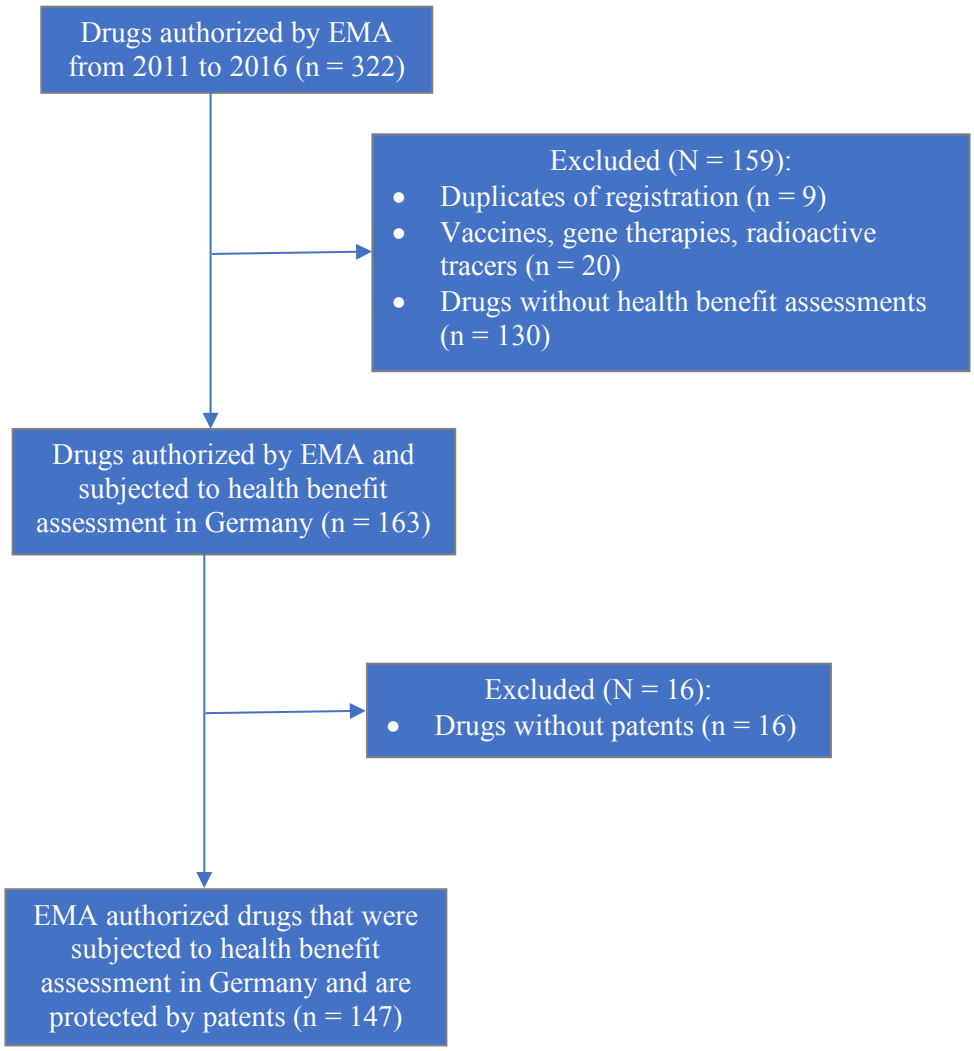

Figure 1 – Construction of the data set

2.5.2 Methodology

The innovativeness of the 147 drugs was measured using the three current measures of radical drug innovation described above: patent backward citations, NME classifications on a stand-alone basis, and NMEs combined with FDA Priority Review designations. Subsequently, the outcomes of the three current measurement methods were compared (using crosstabs analysis and Sankey diagrams) to assess their consistency. Finally, we introduce our new measure and

assess its validity vis-à-vis the three established measures. But first, before comparing, we introduce our four measures.

For the first measure (*Patent Top5*), following the approach proposed by Shane (2001) that was also described in the 2015 OECD working paper *Measuring the technological and economic value of patents* (OECD 2015) and by Dahlin and Behrens (2005), we assessed the radicalness of the 147 drugs using backward citation analysis. According to Shane (2001), an invention is more radical if its underlying patents cite more previous patents in patent classes that are different from the patent classes of the patents that protect the invention. The higher the ratio (between 0 and 1), the more radical the invention is: A radicalness index of 1 means that all patents of the invention cite previous patents that are all in patent classes that differ from the patent classes of the patents that protect the invention. We calculated the radicalness index for each focal patent, and for all other patents granted in the same year and in the same four-digit international patent class (IPC) as the focal patent. If a focal patent was within the top 5 per cent of the Shane radicalness index within the relevant four-digit IPC patent class from the same year in which the focal patent was approved, then we classified the drug as radically innovative, and otherwise as incrementally innovative. We chose the 5 per cent cutoff point because it had been used in previous research (e.g., Singh and Fleming 2010).

For the second measure (*NME*), previous research methods were replicated (e.g., Cohen and Caner 2016; Dunlap et al. 2013; Fernald et al. 2017) to differentiate the 147 drugs into radical or incremental innovations. All drugs with an NDA type 1 classification (i.e., all NMEs) were categorized as radical innovations. All biologics were also categorized as radical innovations because they have been a major driver of important clinical progress in areas of high, unmet medical need. Drugs with NDA classification codes other than type 1 (i.e., non-NMEs) were categorized as incremental innovations.

For the third measure (*NME + Priority Review)*, the 147 drugs were classified into radical and incremental innovations using the NME classification and FDA Priority Review designations. In line with previous research (e.g., Arnold and Troyer 2016; Sorescu et al. 2003; Sternitzke 2010), drugs were categorized as radical innovations if they had a type 1 NDA classification (i.e., all NMEs) or if they were a biologic with an FDA Priority Review. All other drugs with different NDA classification codes and all other drugs without FDA Priority Reviews were classified as incremental innovations.

Finally, the innovativeness of the 147 drugs was assessed using the newly developed measure based on NMEs and the German HTA (*NME + HTA*[10]). All biologics and all NMEs that also carried a designation of a major or considerable additional clinical benefit were categorized as radically innovative. All others were classified as incrementally innovative. *Table 2* provides an overview of all measurement methods used in this study.

Table 2 – This study's operationalizations of radical and incremental innovations

Construct	Radical Innovation	Incremental Innovation
Patent Top5	A drug with a patent within the top 5% of the Shane (2001) radicalness index within the relevant four-digit IPC patent class from the same year in which the focal patent was approved	All other drugs
NME	All type 1 NDA classifications and all biologics	All other NDA classifications
NME + Priority Review	All type 1 NDA classifications and all biologics with FDA Priority Review	All other NDA classifications and all drugs without FDA Priority Review
NME + HTA	All type 1 NDA classifications and all biologics with a major or considerable additional benefit per the Germany HTA	All other NDA classifications and all drugs without a major or considerable additional benefit per the Germany HTA

2.6 Results

2.6.1 Measuring drug innovativeness through current measures

All 147 drugs were classified as either radical or incremental innovations using the previously described current measures, which are based on either novelty (*Patent Top5* or *NME)* or a combination of novelty and therapeutic value (*NME + Priority Review*). As can be seen from the data in *Table 3*, the two measurement approaches based on novelty alone (*Patent Top5* and *NME*) generate considerably different outcomes. When measured through *NME*, 86 per cent of the drugs are classified as radically innovative. However, when they were assessed through the other current measure of novelty (*Patent Top5*), only 33 per cent of the drugs are categorized as radical innovations. Only 45 (36%) of the 126 drugs that are classified as radically innovative using the *NME* approach are also categorized as such by the *Patent Top5* method.

[10] HTA was based on the assessment of the additional therapeutic value of drugs net of treatment risks (safety) when compared to the standard of care (i.e., the best treatment option that was available at the time of the comparison). There were no evaluations of ethical, legal, or social aspects of any drug.

Table 3 – Cross-tabulations of drug innovativeness of *Patent Top5* versus *NME*

			NME		
			Incremental	Radical	Total
Patent Top5	Incremental	Count	17	81	98
		% of Total	11.6%	55.1%	66.7%
	Radical	Count	4	45	49
		% of Total	2.7%	30.6%	**33.3%**
Total		Count	21	126	147
		% of Total	14.3%	**85.7%**	100.0%

The two current measures of novelty (*NME* and *Patent Top5*), when compared to the current measure based on novelty and therapeutic value (*NME + Priority Review*), come with considerably different outcomes as well. As can be seen from the data in *Table 4*, only 69 (55%) of the 126 drugs that are classified as radically innovative using the *NME* only approach are also categorized as such by the *NME + Priority Review* method. The difference in the outcomes between *Patent Top5* and *NME + Priority Review* are even more notable. As shown in *Table 5*, only 26 (38%) of the 69 drugs that are classified as radically innovative using the *NME + Priority Review* approach are also categorized as such by the *Patent Top5* only method.

Table 4 – Cross-tabulations *NME* and *NME + Priority Review*

			NME + Priority Review		
			Incremental	Radical	Total
NME	Incremental	Count	21	0	21
		% of Total	14.3%	0.0%	14.3%
	Radical	Count	57	69	126
		% of Total	38.8%	**46.9%**	85.7%
Total		Count	78	69	147
		% of Total	53.1%	46.9%	100.0%

Table 5 – Cross-tabulations *Patent Top5* and *NME + Priority Review*

			NME + Priority Review		Total
			Incremental	Radical	
Patent Top5	Incremental	Count	55	43	98
		% of Total	37.4%	29.3%	66.7%
	Radical	Count	23	26	49
		% of Total	15.6%	**17.7%**	33.3%
Total		Count	78	69	147
		% of Total	53.1%	46.9%	100.0%

The Sankey diagrams shown in *Figure 2*, *Figure 3*, and *Figure 4* aim to better visualize the differences in outcomes between the different measurement models. Radically innovative drugs are depicted in green boxes, and drugs characterized as incrementally innovative are shown in gray boxes. The size of the boxes and arrows is based on the number of drugs in each category. As can be seen in *Figure 2*, out of the total 147 drugs, 49 (33%) are categorized as

radical drug innovations based on the *Patent Top5* measure, and 126 (86%) as radical drug innovations based on the *NME* measure. From the 98 drugs classified as incremental drug innovations through the *Patent Top5* method, 81 (83%) are categorized as radical drug innovations and only 17 (17%) as incremental innovations through the *NME* method. The Sankey diagrams visualize the very inconsistent measurement outcomes of the three current measures of radical drug innovation: The measures do not seem to assess the same concept.

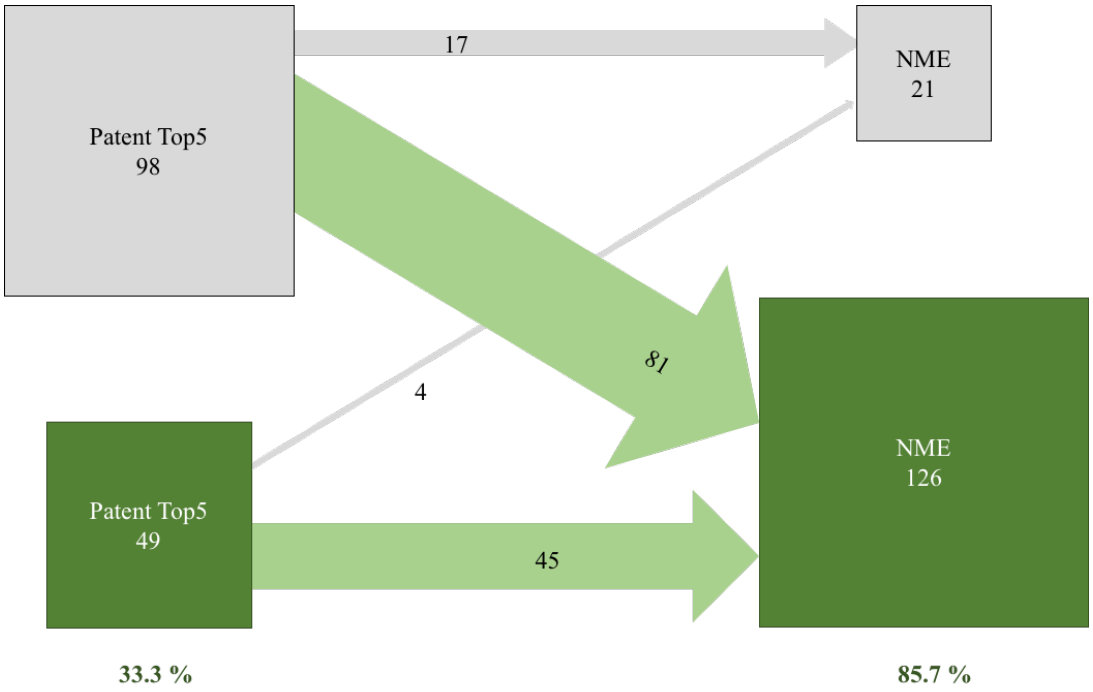

Figure 2 – Differences in outcomes between *Patent Top5* and *NME* (Sankey diagram)

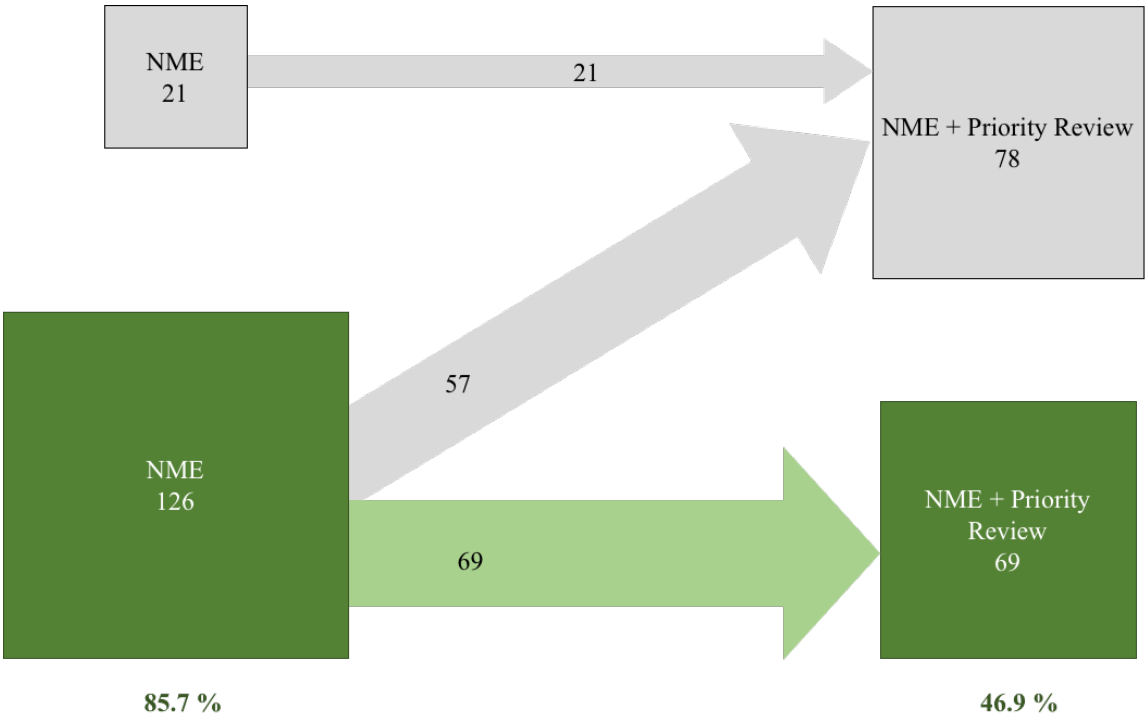

Figure 3 – Differences in outcomes between *NME* and *NME + Priority Review* (Sankey diagram)

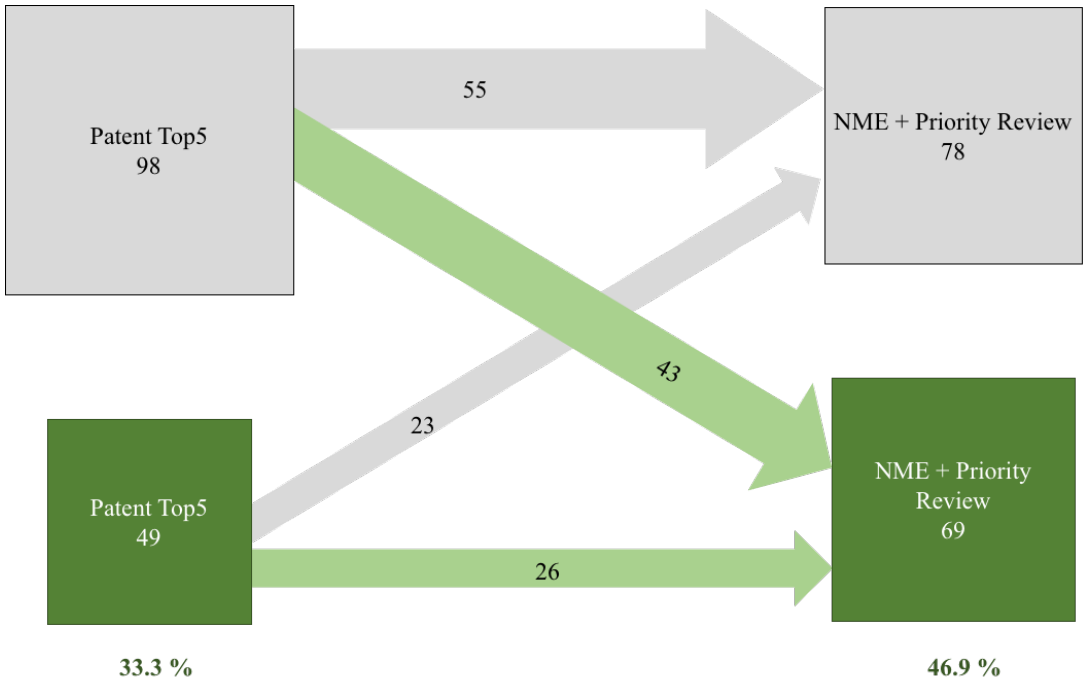

Figure 4 – Differences in outcomes between Patent Top5 and NME + Priority Review (Sankey diagram)

2.6.2 Measuring the radicalness of innovations using the HTA approach

Only 30 of the 147 drugs (20%) qualify as radically innovative when assessed using the newly developed measurement approach that combines NME with HTA (*NME + HTA*; see *Table 6*). Put differently, when using the new measure of radical drug innovation, approximately 80 per cent of the approved drugs do not provide an important additional value versus other existing treatment alternatives. Moreover, from the 69 drugs classified as radical drug innovations through the *NME + Priority Review* method, only 25 (36%) are categorized as radical drug innovations through the *NME + HTA* method (see *Table 6*). Therefore, these two measures show very different outcomes and, as such, cannot be used interchangeably.

Table 6 – Cross-tabulations *NME + Priority Review* and *NME + HTA*

			NME + HTA		Total
			Incremental	Radical	
NME + Priority Review	Incremental	Count	73	5	78
		% of Total	49.7%	3.4%	53.1%
	Radical	Count	44	25	69
		% of Total	29.9%	**17.0%**	46.9%
Total		Count	117	30	147
		% of Total	79.6%	20.4%	100.0%

2.6.3 Two cases

Two cases out of the 147 drugs in the sample are presented below to highlight the outcomes associated with the various measurement approaches that were examined above. Both are typical cases because they represent drugs that got approved by the regulatory authority (FDA) based on clinical trials showing the drugs to be safe and effective in treating the clinical condition of the patient population. As discussed above, to obtain approval from the FDA, it was not necessary to provide evidence of clinical superiority of the new drugs versus already available treatment options. The two cases presented below – regorafenib and trametinib – highlight differences in measurement outcomes.

Regorafenib (trade name: Stivarga®) was approved in 2012 by the FDA (U.S. Food & Drug Administration 2012) and in 2013 by the EMA (European Medicines Agency 2013) for the treatment of metastatic colorectal cancer based on the results of the Phase III CORRECT trial, which showed statistically significant increases in both overall survival (OS) and progression-free survival (PFS) when compared to placebo (U.S. National Library of Medicine 2015). However, in real-world terms, the median overall survival benefit of 45 days was rather modest, and important toxic effects (54% versus 14% in the placebo group) were observed in the trial population (Scheithauer 2012).

Stivarga® is protected by five U.S. patents (7351834, 8637553, 8680124, 9458107, and 9957232). Based on our backward citation analysis, the radicalness indexes of these patents range from 0.24 (patent 9957232) to 0.71 (patent 9458107), but none of the focal patents were within the top 5 per cent of the radicalness index within the relevant four-digit IPC patent classes (A61K, A61P, C07C, and C07D) from the same year in which the focal patents were approved. Consequently, Stivarga® does not qualify as radical. Instead, it is considered to be an incremental drug innovation based on the backward patent citation-based metric.

The FDA categorized Stivarga® as an NME because its active ingredient, regorafenib, had not been previously marketed in the U.S. Moreover, the FDA chose to do a Priority Review of the drug application because regorafenib treats a serious condition and could provide significantly improved effectiveness based on the Phase III CORRECT trial. Thus, when the innovativeness of this drug is assessed using the current approaches of either novelty alone (*NME*) or novelty plus therapeutic value (*NME + Priority Review*), it is classified as a radical innovation.

The mandatory benefit assessment of Stivarga® in Germany in 2013 resulted in a *minor additional benefit* rating for patients suffering from metastatic colorectal cancer when compared to the current best supportive care (Gemeinsamer Bundesausschuss 2016a). This is because the modest gain in median overall survival of 45 days was considered to be partially offset by the additional negative side effect (toxicity) and its impact on the overall quality of life of patients suffering from metastatic colorectal cancer. Hence, when applying the newly developed measure that incorporates the HTA approach (*NME + HTA*), the drug gets categorized as an incremental innovation.

Trametinib (trade name: Mekinist®) was approved by the FDA in 2013 (U.S. Food & Drug Administration 2013) and by the EMA in 2014 (European Medicines Agency 2014) for the treatment of unresectable or metastatic melanoma in adult patients based on the results of the Phase III METRIC trial, which compared Mekinist® versus chemotherapy (U.S. National Library of Medicine 2018). The primary outcome measure of the trial was progression-free survival (PFS), which is a surrogate endpoint. The trial results showed a statistically significant increase in PFS for patients treated with Mekinist®; the median PFS was 4.9 months versus 1.5 months in the chemotherapy group.

Mekinist® is protected by eight U.S. patents (7378423, 8580304, 8835443, 8703781, 9155706, 9271941, 8952018, and 9399021). Based on our backward citation analysis, the radicalness indexes of these patents ranged from 0.07 (patent 8835443) to 0.61 (patent

8952018), but none of the focal patents were within the top 5 per cent of the radicalness index within the relevant four-digit IPC patent classes (A61J, A61K, A61P, C07D, C07C, C07F) from the same year in which the focal patents were approved. Consequently, Mekinist® qualifies only as an incremental drug innovation based on the backward patent citation metric.

The FDA categorized the drug as an NME because its active ingredient, trametinib, had not been previously marketed in the U.S., and no Priority Review had been performed by the FDA. Thus, when the innovativeness of this drug is assessed using the current approach of novelty alone (*NME*), then the drug is classified as a radical innovation. However, when the innovativeness of Mekinist® is assessed using the current measure of novelty plus therapeutic value (*NME + Priority Review*), it is classified as an incremental innovation.

For the mandatory benefit assessment of Mekinist® in Germany in 2015, the therapeutic value of the drug was compared against vemurafenib (trade name: Zelboraf®; Gemeinsamer Bundesausschuss 2016b). It was not tested against chemotherapy as it was in the Phase III METRIC trial, which was the basis of the drug approval by the FDA and the EMA. The benefit assessment resulted in a *considerable additional benefit* rating because the median overall survival increased by 7.6 months for patients treated with Mekinist® when compared with Zelboraf®. Therefore, when applying the newly developed measure that incorporates the HTA approach (*NME + HTA*), the drug gets categorized as a radical innovation.

2.6.4 Validating the newly developed measure

Next, we conducted analyses to examine the extent to which the combination of NME and HTA in our newly developed measure form a construct of radical drug innovation. Following Hair et al. (2019) and Hair et al. (2016), the assessment of formative measurement models, as in our case, differs from approaches for reflective measurement models. Formative measurement models are assessed based on indicator collinearity, statistical significance and relevance of the indicator weights, and convergent validity (Hair et al. 2016). As such, we assessed our recommended *NME + HTA* measure in three steps: Step 1 – Evaluate collinearity of the formative indicators; Step 2 – Assess the indicator weights' statistical significance and relevance; and Step 3 – Assess the convergent validity.

Step 1: To evaluate the collinearity of the formative indicators (see *Figure 5*), the correlation coefficient between *NME* and *HTA* can be computed because there are only two indicators. As shown in *Table 7*, there is no correlation between the two indicators ($r = 0.000$), and thus no collinearity.

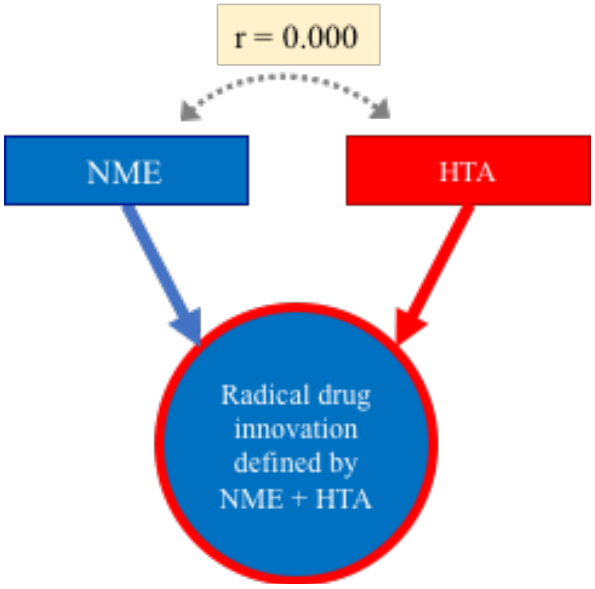

Figure 5 – Formative measure of radical drug innovation (*NME* + *HTA*)

Table 7 – Correlations between *NME* and *HTA*

		HTA
NME	Pearson Correlation	.000
	Sig. (2-tailed)	1.000
	N	147

Step 2: Because the radical drug innovation construct is defined by its formative indicators (*NME* and *HTA*), a regression model with the construct as the dependent variable and the indicators as independent variables should result in significant regression coefficients greater than zero. As can be seen in *Table 8*, both indicators show significant positive correlations with the construct ($p < 0.001$). The total variance explained (R^2) is 86.3%.

Table 8 – Regression coefficients (dependent variables: *NME* and *HTA*)

Model		***Unstandardized coefficients***		***Standardized coefficients***		
		B	***Std. Error***	***Beta***	***t***	***Sig.***
1	(Constant)	-.204	.034		-6.076	0.000
	NME	.238	.035	.207	6.708	0.000
	HTA	.857	.029	.906	29.394	0.000

Step 3: Convergent validity is assessed by the correlation of the measurement model with an alternative measure of the same concept. As shown in *Figure 6*, we chose as an alternative measure of radical drug innovation a combination of *Patent Top5* (as an alternative measure of novelty instead of *NME*) and *Priority Review* (as an alternative measure of the additional therapeutic value instead of *HTA*). The alternative measurement model (*Patent Top5 + Priority Review*) must meet the same requirements as the measurement model to be examined (*NME + HTA*). As such, after repeating Steps 1 and 2 for the alternative measurement model, we conclude that there is no significant correlation between the alternative indicators (r = 0.048; p = 0.563), and thus no collinearity (see *Figure 6*). Both alternative indicators correlate positively and significantly with the construct. The alternative measurement model explains a significant amount of the total variance (R^2 = 0.62). The correlation between our recommended measurement model of radical drug innovation (*NME + HTA*) and the alternative measurement model (*Patent Top5 + Priority Review*) is significant (r = 0.340; p < 0.001). As such, convergent validity is established.

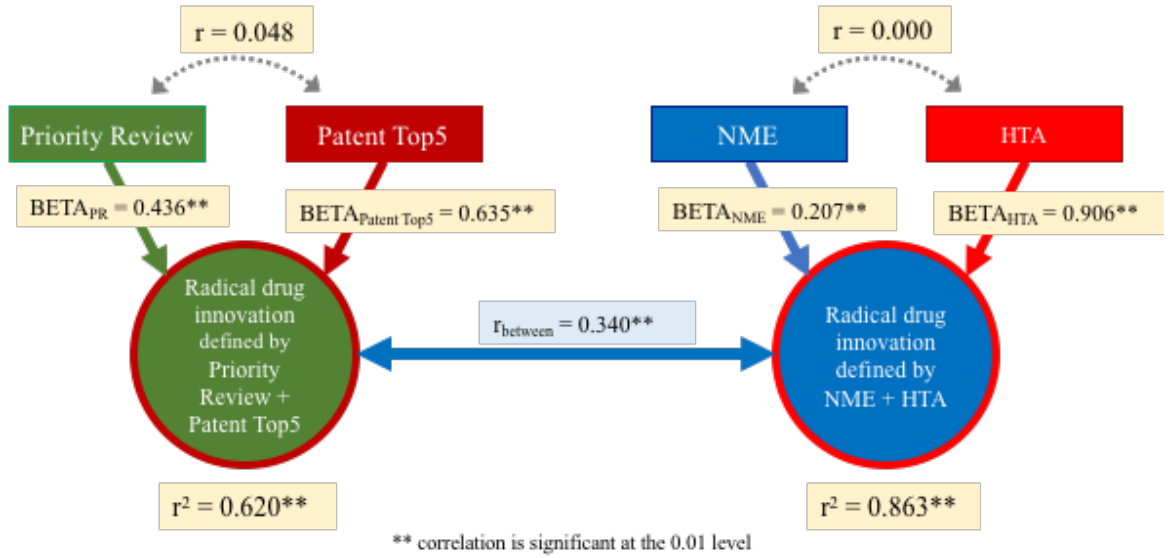

Figure 6 – Convergent validity assessment of the newly developed measure

In conclusion, given that there is no collinearity of the formative indicators (Step 1), both indicators' weights are significant and relevant (Step 2), and the convergent validity is established (Step 3). The newly developed measure *NME + HTA* has been successfully validated.

2.6.5 Relative importance of each of the two indicators of the newly developed measure

Next, the relationship of both construct indicators (*NME* and *HTA*) is examined to test the significance of their relationships with the construct. As noted above, *Table 8* shows that both indicators *NME* and *HTA* are significantly and positively correlated with the radical drug innovation construct ($p < 0.001$). However, the effect of *HTA* on the construct is notably higher (beta = 0.906) than the effect of *NME* (beta = 0.207; see *Table 8*). From this, it is concluded that *NME + HTA* is primarily determined by the *HTA* indicator.

2.7 Discussion

2.7.1 Main insights

Radical innovations are vitally important to many industries (Keupp and Gassmann 2013). We focus on the case of radical drug innovations, which are essential for creating competitive advantages for pharmaceutical firms and for dealing with public health issues in the era of rising healthcare costs. Examination of the factors that enable firms to successfully develop and commercialize radical innovations is of significant interest to both scholars and practitioners. However, radical innovations are challenging to study because of their theoretical, unobservable nature. To date, there has been little agreement in the literature on what exactly constitutes radical innovation and how to measure it appropriately. On the one hand, researchers have used a wide variety of methods to assess innovations, many of which have been subjective and susceptible to biases (Sorescu et al. 2003). On the other hand, a number of researchers have instead utilized large-scale quantitative assessments that presumably offer more objective assessments of radical innovations.

The pharmaceutical industry offers a number of sources for such publicly available data and, as such, is frequently studied by innovation researchers. However, these scholars have tended to use measures of radical drug innovations (i.e., patent citations, NME classifications, and FDA Priority Reviews) without adequate testing and validation. As a result, it remains unclear whether these measures of radical drug innovation actually assess the underlying construct. This undermines our ability to truly and comprehensively understand radical drug

innovations, as well as their antecedents and outcomes. The purpose of the present research is to address this important gap.

This study provides empirical evidence to show that the measures of radical drug innovation currently used in the literature, which mainly emphasize novelty through either patent citations or the use of NME classifications and therapeutic value through FDA Priority Review classifications, show highly inconsistent outcomes. As such, it remains unclear which of the current measurement methods, if any, is appropriate to measure what they purport to measure. Therefore, this study's results further confirm the observation that current measures have not been adequately tested with regard to their precision in assessing radical drug innovation.

Given that the three measurement approaches that currently dominate the literature show such highly inconsistent outcomes, this research considers whether one of the methods is effectively superior to the others with regard to measuring radical drug innovativeness. Following Chandy and Tellis (1998) and Sorescu et al. (2003), we believe that a two-dimensional measure of drug innovation that assesses both novelty and therapeutic value appears to be more appropriate, because a novel drug should also provide important additional benefits to be considered innovative. Therefore, we disagree with Johannessen et al. (2001), who have claimed that novelty is the only relevant innovation dimension that differentiates a radical innovative product from an incremental one. Consequently, we argue that the current novelty-only measures of drug innovation – patent citations and the use of NME classifications on a stand-alone basis – are inherently flawed, and hence should not be used to measure radical drug innovation. This leaves us with the current two-dimensional measure *NME + Priority Review* that assesses both novelty (through NME classifications) and therapeutic value (through FDA Priority Review designations). However, the FDA Priority Review approach is also potentially problematic. The first limitation with the Priority Review assessment is that drugs approved through Priority Reviews might not actually have the clinical outcomes that they were expected to have at the time of the drug application submission. Second, drugs with Priority Reviews may lead to the approval of drugs that carry greater risks than benefits. As such, Priority Reviews should not be used as a measure of radical drug innovation (i.e., as an indicator of the therapeutic value of new drugs).

Given the problems associated with current measures of radical drug innovation, this paper presents a new measure based on the NME classification (as a measure of novelty) and Germany's HTA approach (as a measure of additional therapeutic drug value). Interestingly,

HTA methods, which currently are fully integrated in many healthcare systems, and designed to identify and incentivize new drugs with higher therapeutic value than existing ones, have not yet been adopted by innovation scholars in empirical research. Using this new measurement method, approximately 80 per cent of the approved drugs examined in this study do not provide important additional value versus existing treatment alternatives. This empirical finding strengthens our argument that drug novelty alone does not conclusively indicate whether a drug will deliver extra therapeutic value. Consequently, assessing the comparative therapeutic value of a new drug is critical when assessing its innovativeness. The German HTA method is more appropriate than Priority Reviews to assess therapeutic drug value because it always requires a comparison of the new drug with an existing drug. This is not always the case for Priority Reviews because to get a Priority-Reviewed drug approved by the regulatory authority (FDA), it is not necessary to provide evidence of clinical superiority of the new drug versus already available treatment options. Moreover, the comparison of the measurement results of the two methods (*NME + HTA* versus *NME + Priority Reviews*) shows an important inconsistency between them; thus, both measures cannot be interchanged with each other because they lead to very different measurement outcomes.

Having discovered the utility of the combined *NME + HTA* approach, we then demonstrate the validity of this newly developed measure. We also examine the relative importance of the two indicators that make up this method. We find that radical drug innovations are more strongly characterized by the therapeutic value of a drug (as assessed by the German HTA approach) than by drug novelty / NME. This raises the question of whether the novelty / NME indicator could be removed from our recommended measure of radical drug innovation, which would be an important departure from the theoretical framework discussed earlier in this paper. However, one potential explanation for the lower significance of the NME indicator argues against removing NME from the measure: Pharmaceutical science and technology evolves by "quantum jumps, which are followed by periods of less adventurous steps along the established pathways" (Achilladelis and Antonakis 2001, p. 550). For example, one of these quantum jumps was the discovery of recombinant DNA technology in the 1970s, which led to the foundation of the biotechnology industry, which in turn has brought forward many biological drugs with important therapeutic value. As such, it is likely that the significance of drug novelty becomes more relevant over longer periods of time. The lower significance of the NME indicator in the current study may be explained by the fact that all 147 drugs entered the market between 2011 and 2016, and thus are all probably based on similar

technology platforms. We believe that the NME classification will be likely to play a more significant role for these drugs over time, and hence that the novelty / NME indicator should remain part of our recommended measure of radical drug innovation.

2.7.2 Limitations

As any other, this study is not without limitations. First, innovations were classified into dichotomous categories of radical or incremental innovations, while innovations might be better treated as a continuous variable (Green et al. 1995). However, the fundamental measurement issue addressed in this paper needs to be rectified before fine-tuning the measurement method on a more precise level. Second, the newly developed measure of radical innovation is based on Germany's HTA process. However, the German HTA system, specifically the early benefit assessment that was used for the measurement model, was only recently introduced (in 2011) and has been subject to some methodological criticisms (Herpers and Dintsios 2019). For example, HTA examines a new drug's clinical patient-relevant outcome data such as morbidity, mortality, safety, or quality of life (Schlette and Hess 2013). Conflicting opinions exist, though, about the relevant endpoints for different diseases. For instance, the German early benefit assessment considers overall survival as an endpoint for anti-cancer drugs, while Dabisch et al. (2014) argue in favor of progression free survival (i.e., survival time of patients without advancement of their disease) as an endpoint instead. Moreover, critics have raised concerns about how the Federal Joint Committee (G-BA) selects comparator drugs for the early benefit assessments (Leverkus and Chuang-Stein 2016). For example, sometimes the G-BA chooses comparator drugs that are different from those used in clinical development trials for the new drug or they select comparators that differ from those that were used by other HTA bodies in Europe, which disallows comparisons across countries. Moreover, due to the lack of a benefit assessment (primarily because of low sales), 130 drugs had to be excluded from the original data set. This may further narrow the generalizability of the findings to drugs that have moderate to strong sales. Finally, we had to exclude 16 drugs because they had no patents associated with them.

2.7.3 Suggestions for future research

This study highlights the importance of an appropriate measurement model and proposes a potential new measurement method in an effort to further advance the understanding of radical drug innovation and to inspire additional research on the topic. Additional research is needed to more comprehensively assess the utility of the HTA-based measurement model with regard

to assessing radical drug innovations. This study suggests a need for additional research using the new measurement model to examine the antecedents and outcomes of radical drug innovations, contrasting findings with previous research that was based on different measurement methods. The current study is an important reminder that the field requires appropriate construct definitions that are in line with current practice and that are directly linked to measurement methods, which need to be validated. Having an appropriate measurement model will provide the foundation to further advance the understanding of radical drug innovation. As Brahma (2009) reminds us: "To bring rigor in research, it is therefore, essential for the researcher to first establish an evidence of construct validity before testing the theory" (p. 59).

Chapter 3 | Study 2

Determinants of radical drug innovation: A systematic literature review[11]

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3.1 Abstract

Radical drug innovations are of great importance to pharmaceutical firms and public health. Understanding the determinants involved in successful radical drug innovations is key to increasing this type of output in the future. The objective of this review is to search the literature for key firm-level determinants of radical drug innovation. Following a systematic literature review approach, we considered more than 4,100 peer-reviewed journal articles and PhD theses, 38 of which we included in the narrative synthesis. To guide the review, we use Crossan and Apaydin's (2010) model of firm-level determinants of innovation for the first time within the pharmaceutical industry, which is unique due to the risks, costs, and time frames associated with radical drug innovation. We focus on three groups of determinants: leadership, managerial levers, and business processes. We find the following to be particularly important for radical drug innovation: *external knowledge sourcing* (managerial lever); *internal knowledge management* (managerial lever); *ability of top leaders to innovate, as determined by educational background and professional experience* (leadership); and *leaders' focus on shaping innovation and performance cultures* (leadership). We offer a conceptual framework of critical determinants of radical drug innovation and highlight managerial implications. We also discuss gaps in radical drug innovation research and provide suggestions for future study. Many of the findings discussed in this paper are contradictory because they rely on different definitions and measures, which inhibits our full and accurate understanding of radical drug innovation development. More research is needed to address untested measures of radical drug innovation.

3.2 Introduction

In 2011, a 40-year-old man in certain regions of the United Kingdom was expected to reach a life span of 80.3 years. In 1841, this figure was only 66.6 years (Office for National Statistics 2015). Increases in life expectancy have resulted, in large part, from improved living conditions, access to better nutrition, and significant advances in medical science, including radical drug innovation (Kremer 2002). A notable example of radical drug innovation is Alexander Fleming's discovery of the first antibiotic – Penicillin – in 1928, which was first produced industrially in 1942 by Merck and Pfizer (Achilladelis 1993). Prior to Penicillin, infectious diseases such as pneumonia accounted for high morbidity and mortality worldwide; since then, millions of lives have been and are still saved by antibiotics (Achilladelis 1993; American Chemical Society International Historic Chemical Landmarks 1999).

This example highlights the importance of radical drug innovation for public health. Radical drug innovation is very important to pharmaceutical firms, too, because considerable profits can be made with new drugs, through the mechanism of patent protection (Arnold and Troyer 2016). However, the rate of radical drug innovation has been declining since the second half of the 20th century, despite increasing investments in pharmaceutical research and development (R&D; Gittelman 2016; Horrobin 2000). This is unsettling because approximately two-thirds of the diseases known today still cannot be treated effectively and would likely benefit from increased outputs of radical drug innovations (Claret 2016).

Engaging in the business of radical drug innovation is lengthy, costly, and risky. Although some pharmaceutical firms choose to develop radical drug innovations, others concentrate instead on less risky new drugs with *already validated* targets and mechanisms of action. The latter firms focus on delivering drugs that offer rather limited additional clinical benefits versus existing drugs. For example, Régnier (2013) reports that 58 per cent of the 431 new pharmaceutical drugs approved by the U.S. Food and Drug Administration (FDA) between 1990 and 2004 offered no significant clinical improvements in comparison to drugs that had been already on the market at the time of the approvals. These drugs are sometimes referred to as incremental innovations or *me-too* drugs (Xu and Kesselheim 2014).

Healthcare payers in an increasing number of countries are generally less willing to fund incremental innovations than they are to fund radical ones. This trend begs the question as to how pharmaceutical firms can deliver more radically innovative drugs that extend life, improve the quality of life for patients, are safe, and are effective. What are the factors that allow, enable, and / or incentivize pharmaceutical firms to develop radical innovations? This paper's systematic literature review is inspired by this research question and aims to examine the determinants of radical drug innovation. We believe that understanding these factors is of utmost importance for this industry and for public health – as evidenced by the COVID-19 pandemic – and will help the industry increase their radical drug innovation outputs.

Specifically, the objectives of this paper are to (1) summarize the current state of the art in research on what makes a pharmaceutical firm deliver radical innovations and (2) synthesize the identified determinants into a comprehensive conceptual framework. This is the first systematic literature review on this two-fold topic and, as such, will make important contributions to the existing literature, which is vast and fragmented. Indeed, as Fagerberg et al. already observed in 2005:

> Two decades ago, it was still possible for a hard-working student to get a fairly good overview of the scholarly work on innovation […]. Not anymore. Today, the literature on innovation is so large and diverse that even keeping up to date with one specific field of research is very challenging. (p. 4)

Below, more than fifteen years later, we take up this challenge in order to provide an overview that will offer a platform on which to build future work. That is, the current study follows a systematic literature review approach to map and interpret, in a transparent and reproducible manner, existing knowledge in the fragmented literature on radical drug innovation.

The systematic literature review approach used for this study has been taken from the medical field, which has been facing challenges that are similar to those associated with radical innovation research: large bodies of fragmented knowledge with sometimes contradicting empirical results (Tranfield et al. 2003). Tranfield et al. (2003) define the systematic literature review approach as a "replicable, scientific and transparent process, in other words a detailed technology, that aims to minimize bias through exhaustive literature searches of published and unpublished studies and by providing an audit trail of the reviewers decisions, procedures and conclusions" (p. 209). Both systematic and traditional narrative literature reviews are subject to error and bias. However, the use of a rigorous scientific review methodology reduces the potential for such errors and biases (Cook et al. 1997). This is the key advantage of the systematic over the narrative literature review.

Before we move to our systematic literature review, we will first clarify what we mean by radical drug innovation. Innovation as an outcome can be categorized in various ways. For the purpose of this paper, and following Morgan et al. (2008), we define radical drug innovation as a new pharmaceutical drug that, with acceptable drug safety profiles, improves patient health and addresses unmet medical needs versus existing drugs in ways that were not previously achievable. Radical drug innovations have the potential to extend life despite life-threatening clinical conditions, cure life-threatening clinical conditions, and / or address previously unmet medical needs by offering effective treatments for medical conditions (e.g., rare diseases such as hemophilia) for the first time. This is different from an incremental drug innovation, which is defined here as a pharmaceutical drug that improves an existing drug beyond its primary indication and / or improves other drug properties such as drug administration options. These drugs offer limited clinical benefits over existing ones. Finally, we consider pharmaceutical firms to be both biotechnology and pharmaceutical companies that develop and market

pharmaceutical drugs, either derived from living organisms or from chemically synthesized ones.

3.3 Background

The importance of innovation to the success of national economies, industries, and organizations is well recognized in the literature (Baregheh et al. 2009). Given the broad and significant importance of the topic, innovation has been studied from many different disciplinary and theoretical perspectives, applying a wide range of definitions. As a consequence, and as pointed out by Smith et al. (2008), the innovation literature is highly fragmented. There is neither a dominant discipline nor a theory that can explain all aspects of innovation, including how innovations occur (Dunlap-Hinkler et al. 2010; Fagerberg et al. 2005).

3.3.1 Definitions and measurements

Innovation in a business environment, at its essence, is the commercial use of an invention or new idea (Kanter 1983). Many researchers and organizations have been engaged in the creation of a multi-disciplinary definition of innovation. Baregheh et al. (2009) report in their literature review, which includes about 60 definitions of innovation from 1934 to 2008, that innovation definitions – irrespective of their theoretical and disciplinary origin – predominantly feature the concept of *newness* (e.g., new products, new services, and / or new processes). Similarly, the Organisation for Economic Co-operation and Development (OECD), jointly with the European Statistical Office (Eurostat), has developed the Oslo Manual, which has become the international reference guide for collecting and using data on innovation. The 2018 Oslo Manual (OECD/Eurostat 2019) defines innovation as a "new or improved product or process (or combination thereof) that differs significantly from the unit's previous products or processes and that has been made available to potential users (product) or brought into use by the unit (process)" (p. 20).

There are also some differences across definitions of innovation, many of which are context specific (Kennedy 2009). We mention them here because such differences might lead to different measurement approaches for the concept. However, a comprehensive discussion of these differences goes beyond the scope of this paper. Given our research objective, we limit the discussion here to what Gatignon et al. (2002) refer to as an innovation characteristic: the *degree of newness* of an innovation. In the current literature, the degree of newness of an

innovation is frequently conceptualized dichotomously as either radical or incremental. While radical innovations have been associated with something that is fundamentally new (e.g., a new product or service), thus providing firms with competitive advantages in the marketplace, incremental innovations represent rather smaller and less impactful changes of existing products, services, or processes (Tushman and Anderson 1986). Innovations that are radical are also often referred to in the literature as breakthrough, disruptive, discontinuous, major, or revolutionary (Danneels and Kleinschmidt 2001; Kovacs et al. 2019).

3.3.1.1 Radical innovation

Most of the commonly used definitions of radical innovation have common elements, but there is currently no widely agreed upon single definition of radical innovation in the literature (Green et al. 1995; Kotsemir and Meissner 2013; Kovacs et al. 2019; McDermott and O'Connor 2002). For example, while Forés and Camisón (2016) define radical innovations one-dimensionally, emphasizing newness, as "fundamental changes in the firm's products, processes, technologies and organizational structure and methods" (p. 834), others such as Chandy and Tellis (1998) conceptualize radical innovations two-dimensionally, emphasizing newness and impact, as products that are based on new / different technology *and* better address customer needs when compared to existing options. In their recent systematic review of more than 2,000 papers from three decades of research on radical innovations, Kovacs et al. (2019) confirm this lack of consistency in the definitions of radical innovation. They find that while some scholars define radical innovations entirely through a high degree of newness, others conceptualize radical innovations by both a high degree of newness *and* impact. Such definitional differences lead to varying approaches for measuring the concept of radical innovation.

In general, the measurement of innovation is difficult (Gatignon et al. 2002; Green et al. 1995; Kotsemir and Meissner 2013; Kovacs et al. 2019). It is challenging to measure innovation because it is a theoretical construct or an "unobservable property of objective reality" (Midgley and Dowling 1978, p. 230). As such, to measure it, a clear delineation of the construct is needed in the form of an unambiguous definition. However, the concept of radical innovation is plagued by ambiguous definitions, which leads to different operationalizations and measures of the concept. In addition, as pointed out by Kovacs et al. (2019), "novelty can be assessed as soon as an innovation is conceived, whereas the assessment of impact implies a

process that could span a considerable time period" (p. 21). Thus, measuring impact presents even greater challenges to the already difficult endeavor of assessing radical innovation.

3.3.1.2 Radical drug innovation

There is also ambiguity regarding the definition of what exactly constitutes innovation within the pharmaceutical industry (i.e., radical *drug* innovation; de Solà-Morales et al. 2018; Morgan et al. 2008; Stiller et al. 2020). Radical drug innovation is represented by a wide range of definitions, emphasizing drug novelty, therapeutic benefits, and / or unmet medical needs addressed by a drug. de Solà-Morales et al.'s (2018) literature review examines 36 academic articles and finds 25 different definitions of drug innovation. As was noted above for the concept of radical innovation generally, definitions of radical drug innovation specifically also typically fall into two categories: one-dimensional (based only on drug novelty) or two-dimensional (based on drug novelty and therapeutic benefit – i.e., impact). We believe that, following Stiller et al. (2020) and Morgan et al. (2008), radical drug innovation is best categorized two-dimensionally, capturing both the newness and the therapeutic impact of a new drug because "in addition to being novel, drugs also need to be useful, in that they provide some additional therapeutic value (net of treatment risks) when compared with already existing drugs" (Stiller et al. 2020, p. 7). As such, we define radical drug innovation for the purpose of this research as a new pharmaceutical drug that, with acceptable drug safety profiles, improves patient health and addresses unmet medical needs versus existing drugs in ways that were not previously achievable.

Many scholars have provided ideas about how to differentiate radical from incremental drug innovation. Prior studies have used either patent-based measures (e.g., Hohberger 2016; Phene et al. 2006), New Molecular Entity (NME) designations granted by the U.S. FDA (e.g., Dunlap et al. 2014; Fernald et al. 2017), or priority-reviewed[12] NMEs (e.g., Arnold and Troyer 2016; Dunlap et al. 2016; Kneller 2010; Sorescu et al. 2003; Sternitzke 2010) to delineate radical from incremental drug innovations. However, one major drawback of both patent-based measures and the NME designation is that they emphasize technical newness, but do not address impact in terms of additional clinical benefit. While priority-reviewed NMEs capture both newness and impact, the assessment of the clinical benefit / impact through Priority

[12] Drugs with potentially important therapeutic benefits receive a Priority Review by the U.S. FDA, while all other drugs receive a Standard Review (Sternitzke 2010).

Reviews has important limitations (primarily that shorter review processes lead to greater uncertainty about drug efficacy and safety; Stiller et al. 2020).

It is also important to note that none of these specific measures of radical drug innovation (i.e., patents, NMEs, or Priority Reviews) have been validated (Stiller et al. 2020). Instead, studies using these measures simply state that they have been used in previous studies, implicitly assuming that the measures have been validated. For a more comprehensive discussion on the topic of drug innovation measurement, we refer to Sternitzke (2010) and Stiller et al. (2020).

3.3.2 Firm-level determinants of innovation

There are many different factors that enable firms to innovate. Various literature reviews have attempted to categorize these determinants (e.g., Ahuja and Lampert 2001; Crossan and Apaydin 2010; Slater et al. 2014; van der Panne et al. 2003). Because we could not identify previous literature reviews on the determinants of innovation specifically in the pharmaceutical industry, we opted for the categorization approach of Crossan and Apaydin (2010) as our steppingstone, because theirs has been highly influential for subsequent research over the past decade and is not linked to one specific industry. In their seminal systematic literature review about the state of research on innovation, Crossan and Apaydin (2010) synthesize the various research perspectives into a multi-dimensional framework of organizational innovation. As shown in *Figure 7*, Crossan and Apaydin (2010) identify three distinct groups of firm-level determinants of innovation: leadership, managerial levers, and business processes, each of which we describe briefly below.

Figure 7 – Grouping of firm-level determinants of innovation (Crossan and Apaydin 2010)

3.3.2.1 Leadership

Leadership is particularly important for encouraging learning and innovation within organizations (Pieterse et al. 2010). Various studies have found a positive, direct impact of leadership on innovation (e.g., García-Morales et al. 2008; Makri and Scandura 2010; Matzler et al. 2008). Many scholars have drawn on upper echelons theory (UET) to analyze the relationship between leadership and innovation performance (e.g., Andries and Czarnitzki 2014; Camelo et al. 2010; Wang et al. 2016). The premise of UET is that the experiences, personalities, and values of top management team members impact their decision-making, which in turn influences organizational performance (Hambrick and Mason 1984). In this context, extensive research has examined the role of CEOs and their top management teams with regard to the ability of a firm to innovate (e.g., Cucculelli 2018; Elenkov and Manev 2005; Lin et al. 2011; Makri and Scandura 2010). The research of Yadav et al. (2007) extends beyond characteristics such as a leader's personality, demographics, and leadership style to show that CEOs can influence innovation outcomes by allocating more of their time and attention to activities focused on shaping their firm's future performance.

3.3.2.2 Managerial levers

The resource-based view (RBV) of the firm argues that unique resource allocations at a firm level lead to the creation of innovations (Fagerberg et al. 2005). The knowledge-based view (KBV) of the firm, which is an extension of the RBV, adds that knowledge – and hence organizational learning – is a firm's most important resource for the creation of innovations (Curado 2006). Accordingly, firms need to manage their *resource allocations* and *organizational learning* to create innovations. In this context, several managerial levers have been found to influence the innovation performance of firms.

Because most new knowledge is created outside of individual firms (Fosfuri and Tribo 2008), individual firms need to develop processes to absorb external knowledge. This concept of *absorptive capacity* – a firm's capacity to acquire, assimilate, transform, and exploit external knowledge – has been widely recognized as a key determinant of innovation (Cohen and Levinthal 1990; Lazzeri and Pisano 2014). There is a common understanding in the literature that higher levels of firm-level absorptive capacity lead to better firm-level innovation outcomes. Such firms can effectively access external knowledge in various ways, including through open innovation (e.g., Schuhmacher et al. 2018).

Having a *shared vision* also inspires organizations and team members to learn and to innovate; organizations and teams that lack a shared vision tend to show lower levels of innovation performance (García-Morales et al. 2006; Wang et al. 2004). In addition, the relationship between *organizational culture* and innovation performance has been subject to extensive research. Many studies find that organizational culture significantly impacts the innovation performance of a firm (e.g., Büschgens et al. 2013; Naranjo-Valencia et al. 2011; Sharifirad and Ataei 2012). In particular, strategies that build strong cultures through rewarding results, providing extensive training opportunities, and supporting relational teamwork have been found to enhance innovative performance (Rousseau and Wade-Benzoni 1994).

Finally, the ability of a firm to adjust to the external environment to restore fit (e.g., new competitors or changing customer needs) is argued to be more important for innovation success than the firm's control over, and access to, internal firm resources. This ability is referred to as the *dynamic capability* of firms (Teece et al. 1997). Oskarsson (2003) suggests that dynamic capability is one of the most important success factors of firm-level innovation.

3.3.2.3 Business processes

Innovation is a process to transform an "idea or invention into a product, or into something that has an economic impact" (Hakkarainen and Talonen 2014, p. 63). The innovation process can be examined at different levels (e.g., at the individual firm, industry, regional, or national level). Following our research objective, in this paper, we will discuss the innovation process at the firm level. How this process is organized in a firm is critically important for the development of (radically) innovative outputs (Kahn 2018).

Various attempts to conceptualize the innovation process at the firm level have evolved from simple / linear to complex interactive models with multiple actors and sources, reflecting changes in our understanding of what innovation is over time (Eveleens 2010). First-generation innovation (technology push) models are based on the understanding that the innovation process can be broken down into multiple, sequential phases across a firm's functional areas, each phase ending with a clear a clear go / no-go decision (Cooper 1994). According to this type of model, innovation is conceptualized as the result of basic science outcomes, creating new technologies and, hence, *pushing* innovation (Stefanovska Ceravolo et al. 2016).

Second-generation innovation (need pull) models are similarly broken into linear phases, but also integrate marketing perspectives (i.e., market / customer needs are seen as a key initiator of new ideas that lead to innovation at the firm level; Stefanovska Ceravolo et al.

2016). Moreover, the go / no-go decisions at the end of each phase within need pull models are made by cross-functional teams (as opposed to senior management only) using pre-established go / no-go criteria (Cooper 1994). This type of stage-gate model aims for an "objective assessment of business/technology opportunities and helps synchronize the complex cross-organizational activities that characterize technology generation, development and commercialization" (Cohen et al. 1998, p. 34).

Third-generation (coupling) models combine, or couple, elements of the technology push and need pull models (Stefanovska Ceravolo et al. 2016), recognizing that both new technologies and market / customer needs can be sources of new ideas that lead to innovation. Coupling models are interactive, emphasizing the need for interaction and feedback loops between the linear phases of the innovation process (Stefanovska Ceravolo et al. 2016).

It is with the fourth-generation innovation (integrated innovation process) models that we see a break from the assumption of innovation as a sequential process. The integrated innovation process models perceive that the innovation process runs in parallel with feedback loops across various organizational functions (Rothwell 1992). In addition, these models integrate external knowledge (e.g., from customers, external experts, suppliers, and universities) into the firm-level innovation process (Du Preez and Louw 2008; Tidd 2006).

Fifth-generation innovation (networked) models emphasize that innovation is a process that spans both internal and external networks (e.g., competitors, universities, customers, and suppliers). According to networked models, there are continuous flows of information between internal and external networks, and external networks provide input into the internal innovation process (Du Preez and Louw 2008; Tidd 2006).

Sixth-generation innovation (open innovation) models represent a paradigm shift because according to these models, new ideas (that can be developed into new products or services) can originate in both the internal organization as well as by external partners (Chesbrough et al. 2006; Du Preez and Louw 2008). In addition, these models argue that firms choose to develop such ideas into new product or service innovations either internally or externally. As such, "external ideas and external paths to market [are] on the same level of importance as that reserved for internal ideas and paths to market in the earlier era" (Chesbrough et al. 2006, p. 1).

While the six generations of innovation models have important differences, they also share some similarities. All models start with an idea-generation phase (i.e., searching for innovation ideas resulting from new technologies or from new customer needs), followed by a

project-selection phase (i.e., narrowing down the project options based on a firm's business strategy and business case), during which projects with the highest potential impact and / or feasibility make it to the next phase. Product / service / process development and testing is the next phase, which is very resource intensive and focused on creating a ready-to-use solution that can be brought to market. The final phase of the innovation process is market introduction (Eveleens 2010).

The early innovation phases, during which opportunities are identified and initially assessed (i.e., the ideation and project selection phases), are frequently referred to as the fuzzy front-end innovation (FEI) process (Aagaard 2012; Gassmann and Schweitzer 2014; Hakkarainen and Talonen 2014). The FEI process is a particularly important part of the whole innovation process that needs to be managed differently from the later phases of the process for the following reasons. First, the FEI process deals with very high levels of uncertainty because critical information is still not available (e.g., customer acceptance). As such, decisions to advance or terminate a project need to be made with incomplete information (Herstatt and Verworn 2001). Thus, FEI needs to be managed in a way that risk is accepted, yet minimized. Second, the FEI process determines the speed of the overall innovation project and, as such, its costs (Gassmann and Schweizter 2014). If a project does not fail until later in the process (e.g., in the development phase), significant costs have already incurred. Consequently, one objective for FEI is to fail fast so that the learnings can be applied to future projects, thus increasing the chances that they will succeed. Third, the FEI process is the least structured and understood part of the overall innovation process (Herstatt and Verworn 2001). Following Gassmann and Schweizter (2014), "the front end is poorly understood, and managers experience a lack of knowledge on how to best organize the front end" (p. vi).

It is argued that the FEI process is particularly critical for radical innovations (as opposed to incremental ones; Aagaard 2012; Rice et al. 2001) because the ideas needed for radical innovations are formulated during the fuzzy front-end phase (Nicholas 2014). Consequently, many believe that the FEI process for radical innovations needs to be managed differently than FEI used for incremental innovations (Aagaard and Gertsen 2011; Koen 2004; Reid and De Brentani 2004). The FEI process needs to be sufficiently flexible to accommodate the many uncertainties related to radical innovations because, at this (inception) phase, it is not clear if the idea will eventually turn into a radical innovation or not (Nicholas 2014). As discussed before, radical innovations are defined by their level of newness and impact. While the newness of a product or service can be understood fairly easily, the understanding of the

actual impact of a new product or service can happen only after it is introduced into the market (i.e., there is an important time lag). Although theoretical discussion of the relationship between the FEI process and radical innovations has advanced in recent years, there is still very limited empirical evidence to support theoretical arguments about what differentiates the FEI process for radical and incremental innovations.

3.3.3 Innovation in the pharmaceutical industry

Firm-level innovation processes are industry-specific (Pavitt 2005). As such, they need to be examined through an industry-level lens, taking industry-level contexts into account. Innovation in the pharmaceutical industry (i.e., drug innovation) is particularly unique for a number of reasons. First, drug innovation is primarily science-driven and not, as is the case in most other industries, customer-driven (Aagaard and Gertsen 2011). Second, drug innovation is very costly (Aagaard and Gertsen 2011; Dubey and Dubey 2010; Munos 2009; Petrova 2014). Pharmaceutical firms invest, on average, about 15 per cent of their sales revenues in R&D (Guevara et al. 2015). This is one of the highest ratios of any industry globally. According to some estimates, it costs up to 1.8 billion U.S. dollars to discover, test, and develop a new drug (Mestre-Ferrandiz et al. 2012); this estimate includes the costs of drug candidates abandoned during pre-clinical and clinical testing. To recoup these risky R&D investments, patenting is a particularly important tool within the pharmaceutical industry. According to Sternitzke (2010), approximately 80 per cent of all pharmaceutical products and 45 per cent of all pharmaceutical processes are patented. Third, drug innovation is a very lengthy process. R&D investments are often necessarily high because R&D cycles are long and associated with high attrition rates (which necessitate more funding). It takes, on average, between 12 and 14 years to bring a new drug to market after it has been identified, because it has to go through rigorous testing (Schuhmacher et al. 2016; Sternitzke 2010; Van Norman 2016). The testing process is highly controlled by regulatory authorities such as the FDA in the U.S. and the EMA in the European Union. Finally, drug innovation is risky because most R&D programs in pursuit of new drugs fail. The overall success rates of pharmaceutical R&D are very low. On average, only 5 per cent of drug candidates entering clinical development make it to market (Adams and Brantner 2006; Munos and Chin 2011).

To address these challenges, pharmaceutical firms often design their innovation processes using a unique combination of elements from the generations of innovation models outlined above. Pharmaceutical innovation processes can be broken down into multiple,

sequential phases (which is typical of a technology-push model discussed further below) across a pharmaceutical firm's functional areas, each phase ending with a clear go / no-go decision. Most innovation-related activities in pharmaceutical firms are organized in their R&D functional areas.

3.3.3.1 Research stages

Pharmaceutical research relies on the understanding of biological causes and pathways of a disease (i.e., biological disease understanding). Based on this fundamental disease biology expertise, molecular targets are identified and selected to address the disease. Then, drug discovery searches for potential hits (i.e., lead compounds with sufficient evidence to act on the chosen target; Aagaard 2015), and the selected lead compounds are tested non-clinically for safety, including in laboratory animals.

The research stages (ranging from disease understanding to drug discovery to non-clinical testing) of pharmaceutical innovation typically focus on front-end innovation (FEI). Aagaard (2015) depicts the FEI process in pharmaceutical research as shown in *Figure 8*.

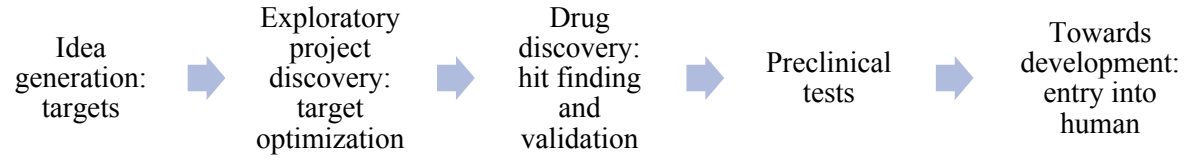

Figure 8 – Front-end innovation process in pharmaceutical research (Aagaard 2015)

The overall objective of the pharmaceutical FEI process is to deliver as many possible drug candidates with "sufficient evidence of biologic activity at a target relevant to a disease as well as sufficient safety and drug-like properties so that it can be entered into human testing" (Mohs and Greig 2017, p. 654). However, because a firm's R&D resources are limited, it is critical to choose and progress through the R&D process with drug candidates that have the highest potential (Aagaard and Gertsen 2011). The selection and subsequent development of drug candidates with the greatest prospects is done using stage-gate models, with the objective to 'kill' unlikely drug candidates as early as possible in the R&D process, before too many resources are used on them (Morgan et al. 2018). For example, after a post-mortem analysis of their successful and failed drug candidates, the British-Swedish pharmaceutical firm AstraZeneca concluded that too many drug candidates had progressed to subsequent stages without sufficiently robust evidence, eventually failing late in the clinical development process

(Cook et al. 2014). In response to this discovery, AstraZeneca formulated what they call a *5R framework* (*r*ight target, *r*ight tissue, *r*ight safety, *r*ight patient, and *r*ight commercial potential) to guide their selection of drug candidates at each stage (Cook et al. 2014). Morgan et al. (2018) report that the application of the 5R framework had a positive impact on AstraZeneca's overall R&D success rates, with more drug candidates advancing to Phase III completion compared to before the framework was used.

The fundamental knowledge required for the FEI phases can be built up internally and / or sourced from third parties. Because most new knowledge is generated outside individual firms, pharmaceutical firms frequently pursue R&D collaborations (networked and open innovation models) with research universities and / or other pharmaceutical firms in an effort to access and integrate critical knowledge needed for radical drug innovation (Sternitzke 2010). In addition to getting access to critical external knowledge, these R&D collaborations also help to reduce the high-risk exposure that is inherently associated with pharmaceutical innovation. For example, through R&D collaborations, pharmaceutical firms can transfer some of the development risks to an external partner, spending fewer in-house resources on drug candidates that do not yet show complete evidence of clinical benefit.

3.3.3.2 Development stages

When a drug candidate successfully progresses through the research-related stages, an Investigational New Drug (IND) application to request approval for clinical testing of the drug candidate in humans is then filed with the regulatory authorities. The development stages aim to advance new drug candidates through clinical trials in humans, before, if the trials are successful, a market authorization can be filed with the regulatory authorities (Petrova 2014). *Figure 9* shows the clinical test phases. Phase I studies are normally the first tests of a drug candidate in healthy volunteers before the drug can be tested in larger studies with patients for which the drug is intended. Phase II focuses on dose finding, and Phase III aims to provide evidence of the drug's effectiveness and safety in large patient populations. Each phase is dependent on the previous one, and each clinical trial determines whether a drug will move forward or not (see Sternitzke (2010) and Petrova (2014) for more detailed overviews).

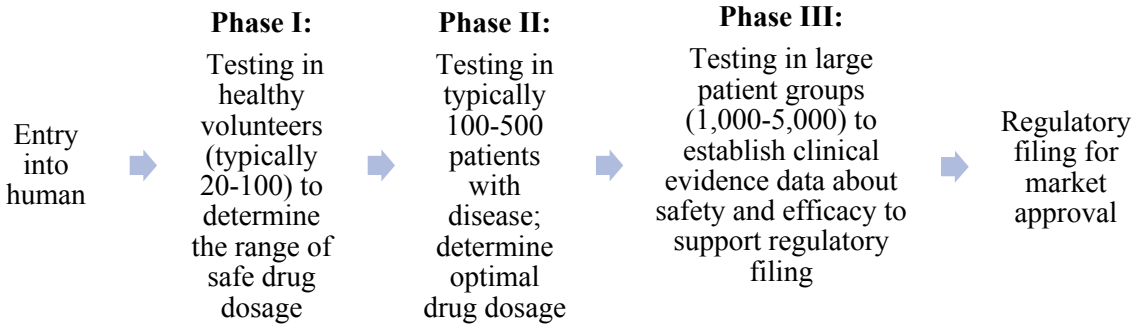

Figure 9 – Innovation process in pharmaceutical development (Petrova 2014)

3.3.3.3 Firm-level determinants of radical drug innovation

In their recent review of more than 600 academic papers on innovation in the pharmaceutical industry, Romasanta et al. (2020) find that, in most studies, the R&D process tends to be treated as a black box and that research has yet to clearly elucidate the detailed innovation processes at work inside the black box. To date, there is only limited empirical evidence available to guide researchers and practitioners regarding which R&D process factors are more likely to lead to successful radical drug innovation outputs (versus incremental ones). In general, it is hard to identify why certain firms are able to develop radical innovations, while others are not. All drug candidates, regardless of their level of innovation (radical or incremental), go through the same R&D process outlined above. Moreover, pharmaceutical R&D is organized in very similar ways across most pharmaceutical firms, including the use of stage-gate models with very similar stages and gates (Aagaard and Gertsen 2011). As a result, the organization of a pharmaceutical firm's R&D process – at a macro level – does not seem to be a distinguishing criterion for radical innovation output. It has been argued that FEI phases are critical for radical drug innovation, but there is only limited empirical evidence to support this (Aagaard and Gertsen 2011). Which begs the question: What firm-level determinants, particularly within the front-end phase of the innovation process, are critical for radical drug innovation?

3.4 Methodology

To answer our research question, this systematic literature review follows the three main phases described by Tranfield et al. (2003) and Bryman and Bell (2015): (1) determine the review questions and plan the review, (2) conduct the review – including the research synthesis, and (3) report the findings. We describe the first two phases in detail below.

The first phase involves determining the review questions and planning the review. The objective of the current systematic literature review is to search the literature for the firm-level determinants of radical drug innovation. The review was guided by the following question: What are key determinants of radical innovation in pharmaceutical firms? A rigorous review protocol was adapted from Gerth (2013) and used as a framework to conduct the current review. The review was limited to peer-reviewed journal articles and PhD theses because they represent validated knowledge. The following databases and search engines were used to find relevant papers: (1) Business Source Premier (EBSCO) database, (2) ProQuest database, (3) Google Scholar search engine (used for forward searches only), and (4) Web of Science database (used for backward searches only). We only searched for papers written in English.

In the second phase, the following search strategy was used to enable a sensitive and effective literature search (i.e., a search that leads to all relevant papers, but limits unnecessary work; see *Figure 10* and detailed description below).

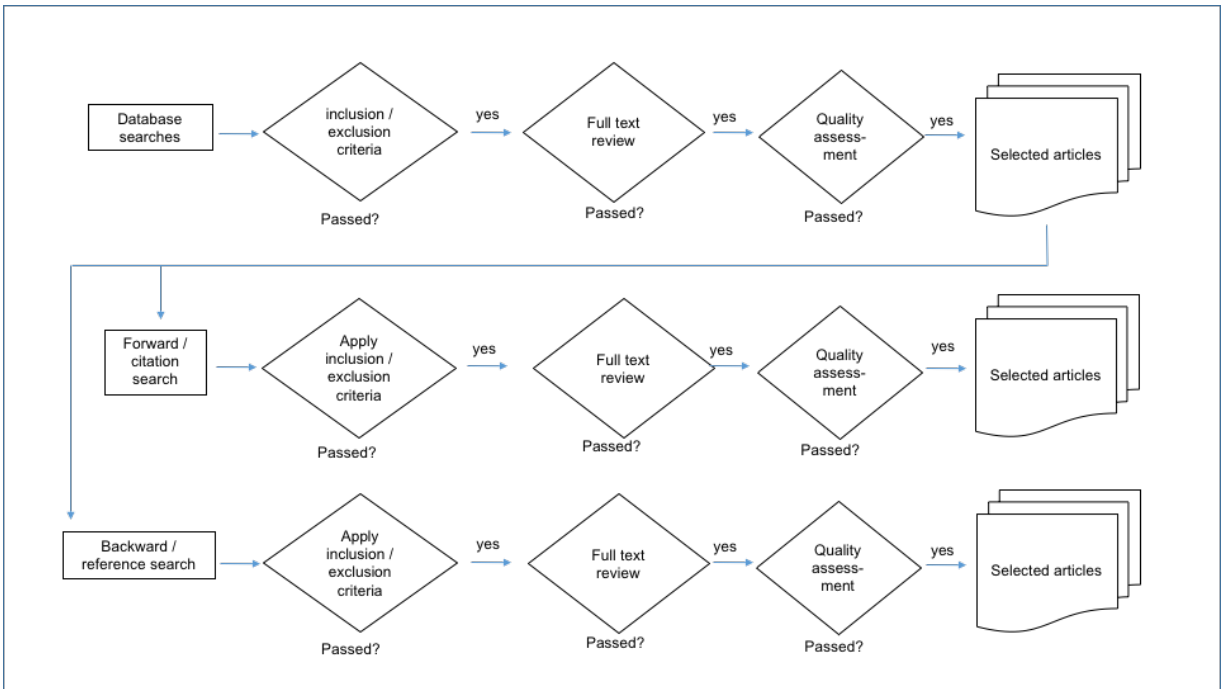

Figure 10 – Search strategy used for the systematic literature review

Step 1: We first identified key words and synonyms that are linked to the review question: *radical innovation* and *pharmaceutical*. These key words were combined into an initial search string, and an initial search was performed in EBSCO to identify other relevant search terms and synonyms. As a result, additional terms such as breakthrough, revolutionary,

biotechnology, and life sciences were added to the search string. The updated string was used for the subsequent searches in the EBSCO and ProQuest databases (see *Table 9*).

Table 9 – Final search strings

Database	Final Search Strings
EBSCO & ProQuest	(TI(Innovat*) AND TI(break* OR radical OR revolution* OR major OR tech*) AND TI(Pharma* OR Biotech* OR "Life Science")) OR (AB(Innovat*) AND AB(break* OR radical OR revolution* OR major OR tech*) AND AB(Pharma* OR Biotech* OR "Life Science"))

Step 2: The identified papers were downloaded into Zotero®. All duplicates were then removed. The titles and abstracts of the remaining papers were reviewed, and each paper was screened in or out based on inclusion and exclusion criteria that were developed based on the review question. These criteria are shown in *Table 10*.

Table 10 – Criteria for screening paper

Components of the Review Question	Inclusion Criteria	Exclusion Criteria
Radical Innovation	• Innovation as an output in the form of a new pharmaceutical drug • Frameworks based on organizational learning, strategy research, and management research theories	• Process innovation • Organizational innovation • Frameworks based on macroeconomic or technological theories
Pharmaceutical Firm	• Empirical data from pharmaceutical firms • Pharmaceutical firms dedicated to research and development	• Contract manufacturers (CMOs) • Pharmaceutical companies fully dedicated to the development and manufacturing of generics and / or biosimilars (e.g., Teva)
Firm Level	• Determinants of innovation at the company level (i.e., the many externally observable determinants such as firm size, ownership structure, etc.)	• Determinants of innovation at the: - industry level - intra-organizational level (e.g., organizational structures and policies) - institutional level (e.g., appropriability regime)

All papers included in this study are, as indicated above, written in English (we excluded all papers written in languages other than English).

Step 3: All remaining papers were entirely reviewed (i.e., full-text review) to evaluate their contributions based on the review question.

Step 4: For all remaining papers, a quality assessment was performed. Quality assessment refers to the "appraisal of a study's internal validity and the degree to which its design, conduct and analysis have minimized biases or errors" (Tranfield et al. 2003, p. 215). Because some of the papers in scope are PhD theses, we assessed the quality of each paper using criteria based on the guidelines for reviewers of the 79th annual meeting of the *Academy of Management* (Academy of Management n.d.), shown in *Table 11*, instead of relying on the overall impact factor or ranking of the journals in which the selected papers were published. These criteria were used by two raters to score all papers in scope (3 = Fully meets the criteria; 2 = Partially meets the criteria; and 1 = Does not meet the criteria). All score differences were discussed until 100 per cent agreement was reached. All papers with an average weighted score of 2.0 or higher were included in the final synthesis.

Table 11 – Quality assessment guidelines

Section	**Criteria**
Theory	• Clearly defined theoretical framework • Hypotheses, if any, are based on outlined theoretical framework • Existing literature references
Method	• Appropriate analytical method • Internal and external validity (in the case of quantitative papers) • Clearly defined and operationalized research variables
Results	• Theory/hypotheses tested adequately and clear presentation of results
Contribution	• Meaningful contribution to the theory, empirical knowledge, or management practice

Step 5: To increase the number of relevant studies, a forward citation search (a search for recent papers that cite the previously published paper of interest) was done for all papers that remained after Step 4. Rigorous evidence identification is fundamental for systematic reviews because this determines the outcome and validity of the study. The search was performed in Google Scholar. Steps 2 through 4 were then repeated for all identified papers.

Step 6: A backward reference search (a search for papers that had been published before the paper of interest was published) was done for all papers that remained after Step 4. The search was performed in Web of Science. Steps 2 through 4 were then repeated for all identified papers.

Step 7: We used a standardized data extraction form for selecting and documenting relevant data from all 38 papers that were finally selected. The data extraction form was

developed *before* the data extraction started and was designed to collect all information needed to address the review question. The same form was used for every paper in scope, so the same type of information was extracted from all studies. In the absence of such a standardized form, there is the risk that researchers subjectively extract information that they perceive as relevant while reading each study. As such, our approach reduced the risk of bias (Kitchenham 2004). The data extraction form used for this systematic literature review included the following information: (1) Title, authors, journal, and publication details; (2) Theoretical foundation of the paper; (3) Type of study (quantitative, qualitative, or mixed methods); (4) Sample size; (5) Definition and operationalization of radical innovation used in the study; and (6) Results (identified determinants of radical innovation in pharmaceutical companies).

Step 8: A narrative synthesis was used to summarize the findings from all of the 38 selected research papers and to highlight important characteristics of the studies, including similarities and differences. The overall objective of the synthesis is to classify the determinants of radical innovation found in the fragmented literature into categories (i.e., to establish a framework that can be used for theory bulding). To do this, we first defined 10 a priori codes based on the frequently discussed firm-level determinants of radical innovation (as discussed in the *Background* section). These codes, shown in *Table 12*, steered the initial analysis of the reviewed papers. As the review proceeded, new codes that emerged were added, existing ones were modified based on the outcome of the analysis, and a priori codes that were not linked to any relevant data were deleted. After the initial coding of the reviewed papers, we grouped and hierarchically structured the identified themes based on the review question and the classification suggested by Crossan and Apaydin (2010; see *Background* section). As a result, an initial template with broader themes (general direction; e.g., managerial levers) and sub-themes (details; e.g., external knowledge sourcing, and / or internal knowledge management) emerged. The initial template was further developed by applying it to, and modifying it for, each additional research paper that was reviewed. As a result, the modified template had to be re-applied to all other reviewed research papers. This iterative process continued until the template covered all relevant themes in all reviewed papers.

Table 12 – A priori codes

1.	Leadership (e.g., Bel 2010; van der Panne et al. 2003; Makri and Scandura 2010)
2.	CEO and top management team characteristics (e.g., Buyl et al. 2011; Daellenbach et al. 1999; Yadav et al. 2007)
3.	Vision and strategy of the firm (e.g., Ritter and Gemünden 2004; van der Panne et al. 2003; Vanhaverbeke and Peeters 2005)
4.	R&D resources (e.g., Hall et al. 2016; Shefer and Frenkel 2005; van der Panne et al. 2003)
5.	Organizational learning (e.g., Chiva et al. 2014; Jiménez-Jimenez and Sanz-Valle 2011)
6.	Organizational culture (e.g., Büschgens et al. 2013; Naranjo-Valencia et al. 2011; Sharifirad and Ataei 2012)
7.	Absorptive capacity (e.g., Cohen and Levinthal 1990; Lazzeri and Pisano 2014)
8.	Dynamic capability (e.g., Breznik and Hisrich 2014; O'Connor 2008)
9.	External collaborations (e.g., De Man and Duysters 2005; Sampson 2007)
10.	Project or portfolio management (e.g., Kock and Gemünden 2016; Mikkola 2001)

3.5 Results

Using the systematic literature review methodology described above, we considered 4,134 peer-reviewed journal articles and PhD theses. Initial results from searches using EBSCO and ProQuest (Step 1 in *Figure 11*) resulted in 1,028 papers, given the rather broadly defined search string. The forward citation search also yielded a high number of citations: 1,788 (Step 6 in *Figure 11*), as did the backward reference search: 1,318 (Step 11 in *Figure 11*).

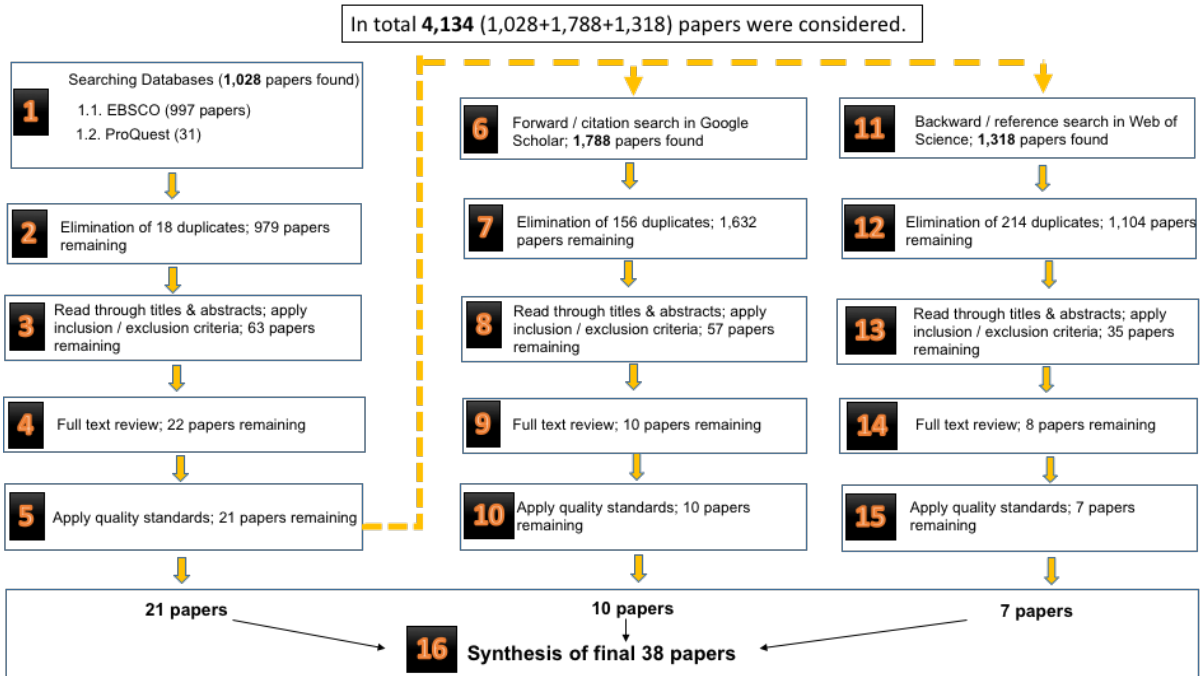

Figure 11 – Results of the systematic literature review screening process

As shown in greater detail in *Table 13*, from the 4,134 papers that were considered, 38 papers (0.9%) were selected for the narrative synthesis (35 peer-reviewed articles and 3 PhD theses). Only 38 papers were included because most of the 4,134 papers do not differentiate between radical and incremental innovations; instead, they examined the determinants of innovation in general. In addition, many papers do not specifically examine the determinants of radical innovation at the firm level. Lastly, many of the papers do not investigate radical innovations in a pharmaceutical or biotech industry setting.

Table 13 – Selection of papers

Database / Search Engine	# of Papers Identified	# of Papers Selected	Selection Rate
EBSCO	997	21	2.1%
ProQuest	31	0	0%
Forward search (Google Scholar)	1,788	10	0.6%
Backward search (Web of Science)	1,318	7	0.5%
Total	**4,134**	**38**	**0.9%**

This systematic literature review is based on fairly recent papers, with 17 of the selected 38 journal articles and PhD theses published in 2015 or later. Moreover, the national origins of the 38 selected papers tend to follow the global footprint of the pharmaceutical industry. More specifically, the authors of almost half (47%) of the selected papers are from the U.S., which is not surprising given that the U.S. is the country with the most pharmaceutical companies, including some of the largest ones in the world.

All 38 papers in scope examine and discuss radical drug innovation. However, as shown in *Table 14*, none of the papers defines what radical *drug* innovation actually is. Instead, roughly half of the researchers (21/38) provide non-industry-specific definitions of radical innovations despite the fact that, as noted by Morgan et al. (2008), "pharmaceuticals are not ordinary goods. Pharmaceutical products have no intrinsic value to patients or to society; rather, their value lies in the health outcomes they generate" (p. 4). Moreover, the other half of the researchers (17/38) do not provide any definition at all.

Table 14 – Definitions and measurement of radical innovation used in each paper

Author(s)	Year	Determinants	Direction of Relationship with Radical Drug Innovation	Definition of Radical Innovation	Measurement of Radical Innovation
Achilladelis	1993	R&D spending	Positive	Based on different scientific principles, technology, or materials which have replaced or competed successfully with existing products	The author assigns certain antibiotic drugs as radical innovation while others are deemed to be incremental innovation; No clear decision or framework for the differentiation
Arnold and Troyer	2016	R&D spending	Positive	No definition	Joint NME and Priority Review count
		Marketing spending	Negative		
Belderbos et al.	2016	R&D alliances with universities: direct collaborations for pharmaceutical companies with a high level of scientific absorptive capacity; indirect collaborations for pharmaceutical companies with a low level of scientific absorptive capacity	Positive	No definition	Patent count
Cammarano et al.	2017a	R&D outsourcing	Negative	Technological originality; generates a new combination of technological components	Patent count
		Purchase of external technology	Positive		
		M&As	Negative		

Author(s)	Year	Determinants	Direction of Relationship with Radical Drug Innovation	Definition of Radical Innovation	Measurement of Radical Innovation
Cammarano et al.	2017b	R&D outsourcing	Negative	No definition	Patent count
		Knowledge stock of an organization	Negative		
Cardinal	2001	Scientific diversity	Positive	No definition	NME count
		Centralization	Positive		
		Formalization	Positive		
		Frequency of performance appraisals	Positive		
		Goal specificity	Positive		
		Rewards / recognition for output	Positive		
Cohen and Caner	2016	R&D alliance network (heterogeneous knowledge)	Curvilinear	Advance the state of the technology or represent a completely new type of product	NME count
		Knowledge stock of an organization	Positive		
DiMasi	2000	Internal R&D	Positive	No definition	NME count
		Therapeutic area focus	Positive		
Dunlap-Hinkler et al.	2010	Firm size	Positive	Radical innovations start the cycle of technological change	NME count
		Prior radical innovations	Positive		
		Prior incremental innovations (generics)	Negative		
		Joint ventures / strategic alliances	Positive		
Dunlap et al.	2014	Cross-national knowledge from intra-firm sources	Positive	The degree of novelty or change embedded in the innovation; needs to be new to the market	NME count
		R&D spending	Positive		

Author(s)	Year	Determinants	Direction of Relationship with Radical Drug Innovation	Definition of Radical Innovation	Measurement of Radical Innovation
Dunlap et al.	2016	R&D alliances	Positive	Scientific novelty	Joint NME and Priority Review count
		M&As	Negative		
Eslaminosratabadi*	2018	R&D alliances with universities and other biotech firms	Positive	New product that incorporates a substantially different core technology and offers significantly higher benefits to customer	Joint NME and Priority Review count
		R&D alliances with other, larger pharmaceutical firms	Negative		
Fernald et al.	2017	M&As of (start-up) biotechs	Negative	No definition	NME count
		M&As of other, larger pharmaceutical firms	Positive		
		R&D alliances with (start-up) biotechs	Positive		
		Firm size	Positive		
Jong and Slavova	2014	Open science strategies (publication in science journals and joint ventures / alliances)	Positive	A genuinely new product	NME count
		Firm size	Positive		
		Firm age	Positive		
		Knowledge stock of an organization	Positive		
Kamuriwo et al.	2017	R&D alliances	Positive	Products that create entirely new markets or radically change existing ones	Patent count

Author(s)	Year	Determinants	Direction of Relationship with Radical Drug Innovation	Definition of Radical Innovation	Measurement of Radical Innovation
Karamanos	2012	R&D alliances (direct ties)	Curvilinear	The creation of technological knowledge that falls outside the firm's existing know-how	Patent count
		R&D alliances (embedded in a dense network)	Curvilinear		
Karamanos	2014	R&D alliances (firm's partner's centrality in the network)	Positive	No definition	Patent count
Karamanos	2016	R&D alliances (firm's partner's centrality in the network)	Positive	The creation of technological knowledge that falls outside the firm's existing know-how	Patent count
		R&D alliances (indirect ties or structural holes)	Positive		
		Firm size	Positive		
Keyrouz*	2013	Market orientation (customer orientation and technological orientation)	Positive	High level of newness and high level of customer need fulfillment	Joint NME and Priority Review count
Malva et al.	2015	Basic science	Positive	Inventions with a high impact on subsequent inventive activity	Patent count
Park and Tzabbar	2016	Venture capital funding (for early-stage R&D ventures)	Positive	Recombination of knowledge components that is new in a given industry	Patent count
		CEO's structural power	Positive		
Phene et al.	2006	Technologically distant knowledge of national origin	Curvilinear	No definition	Patent count
		Technologically proximate knowledge of international origin	Positive		
Qi Dong et al.	2017	R&D alliances (with other central organizations in an alliance network)	Curvilinear	Paradigm shifts in technological trajectories; can lead to the creation of new customers and new markets	Patent count

Author(s)	Year	Determinants	Direction of Relationship with Radical Drug Innovation	Definition of Radical Innovation	Measurement of Radical Innovation
Quintana-García and Benavides-Velasco	2011	R&D alliances (access to complementary technology)	Positive	No definition	NME count
		Firm size	Positive		
		R&D spending	Positive		
Singh and Fleming	2010	Internal R&D collaboration (team affiliation and organization affiliation vs. being a lone inventor)	Positive	No definition	Patent count
Sorescu et al.	2003	Firm size (sales, assets, profits)	Positive	Novel technology plus substantial customer benefits	Joint NME and Priority Review count
Sternitzke	2010	Basic research	Positive	Novel technology plus substantial customer benefits	Joint NME and Priority Review count
		Knowledge stock of an organization	Positive		
Supriyadi *	2013	Firm's resources (e.g., technology and talents) and culture	Positive	No definition	NDA counts
Suzuki	2018	Organizational slack	Positive	Identifying or generating new knowledge that is beyond the scope of current business	NME counts
Suzuki and Methe	2014	Local search (i.e., searching for new knowledge in close distance to the existing knowledge of a firm)	Positive	No definition	NME counts
		R&D spending	Positive		
		R&D alliances (frequency)	Positive		
Tzabbar and Margolis	2017	Educational heterogeneity of founding team	Positive	No definition	Patent count
		Founding experience	Positive		

Author(s)	Year	Determinants	Direction of Relationship with Radical Drug Innovation	Definition of Radical Innovation	Measurement of Radical Innovation
Watts and Hamilton	2013	Applied science	Positive	No definition	Therapeutic evidence (TE) codes from the FDA's *Orange Book*
		M&As (only for firms dedicated to basic science)	Positive		
Wuyts et al.	2004	R&D spending	Positive	Different core technology; provide substantially greater customer benefits than previous products in the industry	Joint NME and Priority Review count
		R&D alliances (repeated partnering)	Positive		
		Technological diversity	Positive		
Xu	2015	Knowledge breadth	Curvilinear	Incorporation of significantly new technology into product offerings; offer substantially improved product benefits to serve customer needs	Joint NME and Priority Review count
Xu et al.	2013	R&D alliances	Negative	No definition	Joint NME and Priority Review count
		Internal technological knowledge strength	Curvilinear		
Yeoh and Roth	1999	R&D spending (direct impact)	Negative	No definition	NME count
		M&D spending (sales force)	Positive		
Zheng and Yang	2015	R&D alliances (repeated partnering)	Curvilinear	High-impact innovations with the potential to introduce new technological trajectories or paradigm shifts	Patent count
Zucker et al.	2002	R&D alliances (with star scientists at leading universities)	Positive	No definition	Number of research articles written jointly by corporate and star scientists

*: PhD Thesis

In addition to the lack of a clear and unambiguous definition, there is an additional fundamental challenge associated with the operationalization of radical drug innovation: How to objectively measure the radicalness of an innovation, given its unobservable nature? This fundamental challenge has been addressed by researchers in different ways. In the 38 papers used for the narrative synthesis, as shown in *Table 14*, the following methods were mainly used: (1) *patent* counts (14/38), (2) counts of *New Molecular Entity* (NME) classifications (11/38) by the FDA, and (3) joint counts of *NME* and *FDA Priority Review* classifications (9/38).

First, the use of *patents*, which are based on inventions, as a proxy for (radical) innovation is the most common measurement method. Studies that use this approach typically assume that a patent (i.e., invention) will be successfully commercialized at some point in the future. However, such an assumption is questionable because not all highly cited patents lead to commercial products (Malva et al. 2015).

Second, the *NME* classification is assigned to drugs by the FDA's Center for Drug Evaluation and Research (CDER) after successful review of New Drug Applications (NDA; see, e.g., Fernald et al. 2017; Sternitzke 2010). In order to designate a chemically synthesized drug with a type 1 classification (i.e., NME), the FDA requires that the drug contain active substances that have not previously been marketed in the U.S. All other drugs (e.g., drugs that are based on new formulations of previously approved active substances) receive a different (i.e., non-NME) classification by the FDA. Recent studies have categorized NME drugs as radically innovative and non-NME drugs as incrementally innovative (e.g., Cohen and Caner 2016; Dunlap et al. 2014; Fernald et al. 2017).

Third, in addition to the NME designation, the FDA provides an assessment of the therapeutic potential of new drug applications. New drugs with a high potential receive a *Priority Review*, while all other drugs are reviewed within a standard time frame (Sorescu et al. 2003). Researchers who have used this method associate NMEs with a Priority Review as radically innovative drugs and all others as incrementally innovative (e.g., Arnold and Troyer 2016; Dunlap et al. 2016; Sorescu et al. 2003; Sternitzke 2010).

3.6 Narrative synthesis

Pharmaceutical firms can make considerable profits with new, patent-protected drugs (Arnold and Troyer 2016). As such, there are clear economic incentives to develop and commercialize radical innovations in the pharmaceutical industry (Dunlap-Hinkler et al. 2010; Suzuki and

Methe 2014). However, there is considerable ambiguity around the firm-level determinants that enable a pharmaceutical company to develop such radical innovations (Dunlap-Hinkler et al. 2010). But understanding these determinants is key to increasing the output of successful radical drug innovations. Clearly the literature on the topic is incomplete. As noted by Sorescu et al. (2003), if these determinants were already sufficiently identified and fully understood in the literature and in practice, why are the majority of radical innovations represented by only a small percentage of pharmaceutical companies?

This ambiguity was considerable when we analyzed the 38 selected papers. We identified various determinants of radical innovation that were used in multiple papers. Most of these determinants are closely related. Thus, we grouped the determinants according to Crossan and Apaydin's (2010) classification and the procedure outlined in Step 8 above. *Figure 12* displays the grouped determinants.

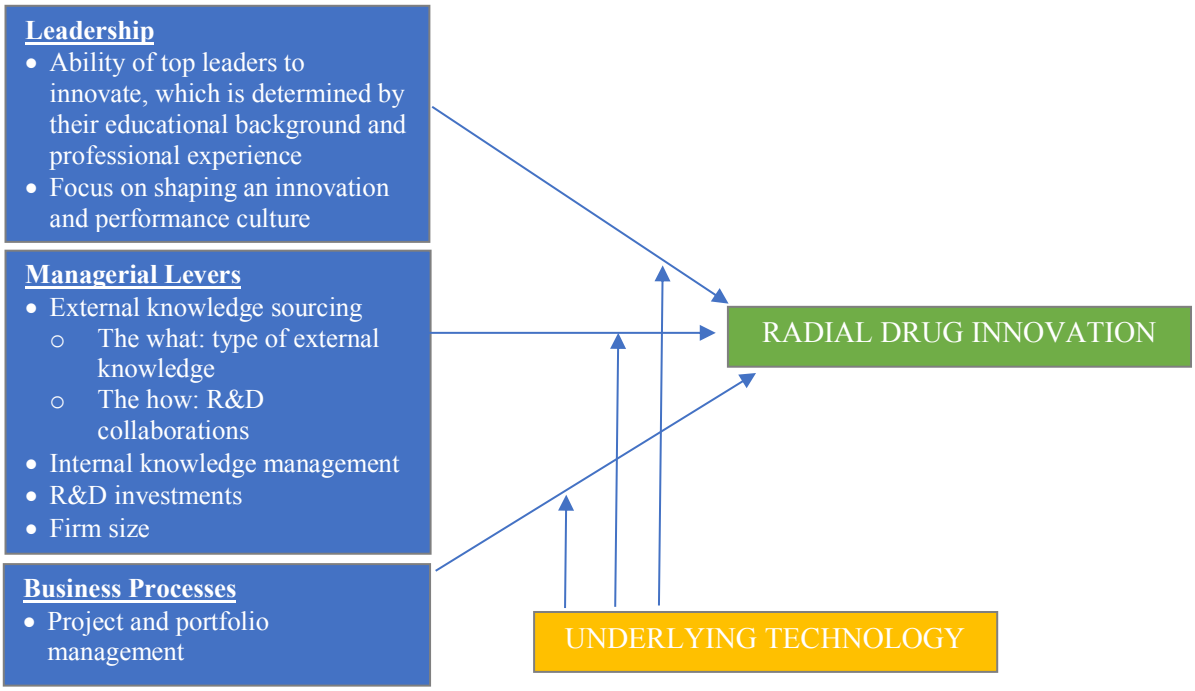

Figure 12 – Model for the determinants of radical drug innovation

We also argue that the underlying pharmaceutical technology of the firm appears to be a moderator of these relationships because "the way innovation is organized, as well as its economic and social effects, depends critically on the specific nature of the technology in question" (Fagerberg et al. 2005, p. 6). We know that pharmaceutical science and technology evolves by "quantum jumps, which are followed by periods of less adventurous steps along the established pathways" (Achilladelis and Antonakis 2001, p. 550). As such, the moderating

effect of technology on radical innovation should be rather small in the periods between these quantum jumps. Nevertheless, we decided to keep underlying pharmaceutical technology in the model (shown in *Figure 12*) to explore the potential moderating effect of technology on radical drug innovation over time.

3.6.1 Leadership

Some researchers note the important role that individual characteristics of leaders play in determining organizational outcomes, including radical innovation within the pharmaceutical industry. With regard to the role that leadership plays in firms' radical drug innovations, two determinants surfaced during our literature review: the *ability of top leaders to innovate, which is determined by their educational background and professional experience* as well as their *focus on shaping an innovation and performance culture within their firms*.

3.6.1.1 Firm leaders' ability to innovate, determined by their educational background and professional experience

Key leaders of pharmaceutical firms need to maintain an in-depth understanding of the tremendous and rapid scientific progress taking place within the pharmaceutical industry. It is only with an appropriate understanding of science and technology, acquired through education and professional experience, that CEOs and other senior leaders can make well-informed decisions about how much to invest in R&D, and more importantly, which specific drug candidates to invest in. And these decisions play critical roles in the development of radical drug innovations. A number of researchers note that leaders' educational and professional experiences play a key role in pharmaceutical innovation within their firms (Supriyadi 2013). In addition, Tzabbar and Margolis (2017) provide evidence that both the educational heterogeneity within the founding team (i.e., the range of advanced degrees held by founding team members) and the number of founding team members with previous founding experience have a positive relationship with radical drug innovation.

Both Supriyadi (2013) and Tzabbar and Margolis (2017) note, however, that their findings depend on a firm's developmental stage. Supriyadi (2013) argues that leadership from CEOs and Chief Scientific Officers (CSOs) is pivotal in early-stage research outcomes, but is less important during later drug development stages (where the goal is to turn a new drug candidate into a marketable drug). According to Supriyadi (2013), the research stage is "precisely the kind of activity for which strategic leaders' influence matters most" (p. 35), while the later, drug development-focused stage (which is highly regulated) leaves less room

for strategic leaders to influence outcomes. It follows then that because early-stage, research / FEI-oriented pharmaceutical firms (pharmaceutical start-up firms) focus more on research than do large firms (which pay attention to drug development in addition to research), the impact of CEO and CSO leadership is particularly important in early-stage, research-oriented pharmaceutical firms. This is supported by research showing that start-up firms in the early research phase are more likely to innovate when they have CEOs who have played a role in founding their firms and who have a lot of previous founding experience (Tzabbar and Margolis 2017). Moreover, Tzabbar and Margolis (2017) find that these characteristics have a negative impact on innovation among start-up firms in later stages of their development. Based on their research, both Supriyadi (2013) and Tzabbar and Margolis (2017) highlight the importance of considering a firm's development stage when examining the influence of leadership on innovation within the firm.

3.6.1.2 Firm leaders' focus on shaping their firms' innovation and performance cultures

A number of the studies in this review also point out that leaders have important impacts on their firms' environments and cultures that are, in turn, associated with radical innovation. For example, Supriyadi (2013) highlights the important relationship between leadership and a culture of diversity, noting that "research has generated relatively consistent findings on how leaders can affect creativity and their firms' inventive success, and much of it seems relevant to managing and benefitting from diversity" (p. 37). Dunlap et al.'s (2014) findings regarding the connection between a culture of intense knowledge-sharing between divisions, centers, and employees and radical innovation suggest the importance of firm leadership in developing and sustaining this type of company culture. In addition, Cardinal (2001) shows that behavior controls (e.g., centralization, formalization, and frequency of performance appraisals) and output controls (e.g., goal specificity; emphasis on output, rewards, and recognition), which are often imposed by a firm's leadership, support radical innovation by enabling scientists to focus on their work and to be productive in ways that align with company goals.

3.6.2 Managerial levers

The vast majority of the 38 studies in our sample (33/38) examine the relationship between managerial levers and radical drug innovation. Results from this literature review indicate that *external knowledge sourcing, internal knowledge management, R&D investments*, and *firm size* are frequently examined managerial levers of radical drug innovation.

3.6.2.1 External knowledge sourcing

External knowledge sourcing is the most frequently examined managerial lever in the studies included in this literature review. Research indicates that a significant amount of knowledge tends to be created outside of individual firms (Fosfuri and Tribo 2008), and that there is a strong connection between external knowledge and successful drug innovation (Jong and Slavova 2014). Scientific advances are usually driven by research universities as well as pharmaceutical and biotechnological start-up firms that are dedicated to the understanding of basic sciences (Achilladelis 1993; Zucker et al. 2002). Gaining and maintaining access to this type of new, transformational knowledge is critical for the survival of firms and is key to developing successful radical drug innovations (Cammarano et al. 2017b; Kamuriwo et al. 2017; Phene et al. 2006). Thus, firms that develop radical drug innovations are more likely than those that do not to effectively identify, acquire, and integrate external knowledge (i.e., absorptive capacity, as discussed in the *Background* section of this paper). Firms with high levels of absorptive capacity are better able to access external knowledge, which, in turn, can lead to radical drug innovations.

The what: Type of external knowledge

External knowledge can either be very different from (heterogenous) or quite similar to (homogeneous) the existing knowledge stock of a firm. On the one hand, through access to heterogenous external knowledge, the absorbing firm can avoid internal knowledge traps (e.g., familiarity traps, or the tendency to favor new knowledge that is familiar versus unfamiliar), thereby making the company more likely to eventually develop radical innovations (Quintana-García and Benavides-Velasco 2011; Wuyts et al. 2004). On the other hand, Suzuki and Methe (2014) find that access to homogenous external knowledge has a positive impact on subsequent radical drug innovations through knowledge accumulation. Phene et al. (2006) show the same relationship between homogenous external knowledge and radical innovations, but only if the external knowledge is sourced globally.

The how: R&D collaborations and mergers & acquisitions

The findings from this literature review also suggest that *how* a pharmaceutical firm sources external knowledge has an impact on the firm's ability to develop radical drug innovations. External knowledge can be accessed through *R&D collaborations* or *merger & acquisitions*, each of which having a differential impact on radical innovation.

Knowledge creation in the pharmaceutical industry is expensive, risky, and time consuming, making it very challenging for a single company to comprehensively create knowledge on its own (Karamanos 2016). Because of this, pharmaceutical firms frequently collaborate with other pharmaceutical companies, universities, and / or public research institutes (Cohen and Caner 2016; Fagerberg et al. 2005; Karamanos 2016; Quintana-García and Benavides-Velasco 2011). Through R&D collaborations, participating parties can effectively combine internal with external knowledge (Jong and Slavova 2014).

Alliances with other pharmaceutical companies, universities, and / or public research institutes are likely to lead to an increase in radical drug innovations through several mechanisms, most notably the exchange of knowledge. Dunlap-Hinkler et al. (2010) argue that alliances bring about synergistic learning opportunities, knowledge development, and creative solutions; partners effectively learn from each other and are inspired toward greater creativity (Cammarano et al. 2017b; Cohen and Caner 2016; Jong and Slavova 2014; Quintana-García and Benavides-Velasco 2011). Cohen and Caner (2016) show that when firms partner with organizations that have unique technological expertise, they increase their likelihood of developing radical drug innovations. They claim that their results "support the premise in network research that alliances as means of accessing heterogeneous knowledge enable focal firms to shift dominant mental models, alter risk perceptions, and engender variation in established routines during converting their inventions into innovations" (p. 13). Furthermore, firms that collaborate with external partners can spend more time and resources on their core competencies, while gaining knowledge and capabilities from their partners (Cammarano et al. 2017b).

External knowledge can be accessed either directly through R&D alliances or joint ventures with other pharmaceutical companies and / or research universities (*direct ties*) or indirectly through other pharmaceutical companies that have direct relationships with research universities *(indirect ties*). In the current review, we find that pharmaceutical drugs developed through direct ties are more likely to be radically innovative (especially when the collaborations take place during the discovery phase of new drug; Eslaminosratabadi 2018; Jong and Slavova 2014; Zucker et al. 2002) than are drugs developed solely by one firm (Cammarano et al. 2017b; Dunlap-Hinkler et al. 2010; Fernald et al. 2017; Quintana-García and Benavides-Velasco 2011). Both Belderbos et al. (2016) and Karamanos (2012) show that pharmaceutical companies with direct ties to universities deliver more radical innovations than do firms with indirect ties. They surmise that indirect ties are less effective because critical

information that emanates from these ties may get misinterpreted or lost as it passes through the various partners in the networks (Belderbos et al. 2016; Karamanos 2012). Moreover, absorptive capacity is key to getting the most out of direct ties with universities and to turning these opportunities into radical innovations. Belderbos et al. (2016) claim that firms with "high scientific absorptive capacity can rely on in-house scientists to perform a critical brokerage role" (p. 16), thereby effectively accumulating and leveraging external knowledge from direct ties.

Collaborations with university scientists and research institutes, in particular, are associated with increases in radical drug innovations (Cammarano et al. 2017b; Jong and Slavova 2014). Partnerships between firms and university scientists allow firms to increase their organizational learning, scientific knowledge, and absorptive capabilities; gain access to cutting-edge information and knowledge networks; improve their ability to recruit high-quality scientists into the firm; and identify and position themselves as an organization with strong scientific competencies (Cammarano et al. 2017b; Jong and Slavova 2014). Zucker et al. (2002) believe that actual (remunerated) collaboration with university scientists (rather than just mere proximity to them) is the primary factor that drives radical drug innovations. They argue that collaboration is key because new knowledge is tacit / uncodified, and thus difficult to transfer. Hence, Zucker et al. (2002) claim that knowledge spillovers within the pharmaceutical industry do not occur simply due to proximity. This insight is in conflict with other empirically supported claims of general knowledge spillover effects (e.g., Dunlap et al. 2014). In addition, firms that engage with universities and / or public research institutes are often able to leverage the extensive networks of their partners (Jong and Slavova 2014).

The experience that a pharmaceutical firm has with managing R&D collaborations seems to positively impact the firm's ability to develop radical innovations (Karamanos 2016), particularly when R&D alliances are repeated with the same partner (Wuyts et al. 2004). Managing alliances can be difficult due to the frequent information asymmetry between the partners. The more that alliance partners are skilled at managing this information asymmetry, the more effective their alliances will be. This, in turn, will enable better knowledge flows between the alliance partners, which will increase the likelihood of achieving radical innovations. However, Zheng and Yang (2015) report an inverted U-shaped relationship between the number of repeated alliances and radical innovations. That is, they reveal a positive relationship between the number of repeated alliances and radical innovations, but only up to a point. If a firm does partner with another firm in too many new R&D projects over longer

periods of time, then the two partners might become too familiar with each other and may favor new knowledge that is already well understood by both firms. This leads to a lower number of radical innovations over time. This finding suggests that familiarity traps might also exist in R&D alliances.

In addition, Quintana-García and Benavides-Velasco (2011) and Eslaminosratabadi (2018) highlight the importance of choosing the *right* partner when entering into a strategic alliance. They argue that innovation benefits that result from R&D collaborations depend on how mutually rewarding and complementary the partners are able to be to one another. More specifically, Quintana-García and Benavides-Velasco (2011) show that partners engaged in complementary technologies are more likely than those focused on similar or dissimilar technologies to develop radical innovations. The idea is that "similarities in knowledge facilitate incremental renewal, while complementarities would make discontinuous strategic transformations more likely" (Quintana-García and Benavides-Velasco 2011, p. 1058).

In addition to R&D collaborations, mergers and acquisitions (M&A) occur frequently in the pharmaceutical industry (Hornke and Mandewirth 2010). Typically, larger pharmaceutical companies acquire other pharmaceutical companies and start-ups to fill their internal R&D pipelines (Cockburn 2004). Findings from the current literature review suggest that the *acquisition* of pharmaceutical firms in order to access their knowledge, particularly their innovative R&D development projects, generally has a negative impact on subsequent radical innovation performance (Cammarano et al. 2017b; Dunlap et al. 2016), possibly because of organizational post-merger integration problems such as inadequate data and information-technology integration, as well as employee disengagement. As noted by Cammarano et al. (2017a), "the advantages of performing M&As may be balanced or outweighed by many issues, such as information asymmetries deriving from the challenging integration of the acquired firm's embedded knowledge, difficulties in synergy realization, cultural distances between companies and technical incompatibility" (p. 8). As such, M&As hinder radical drug innovations.

3.6.2.2 Internal knowledge management

There are different ways in which pharmaceutical firms can create new knowledge that may eventually lead to radical drug innovations. One approach involves investing in pharmaceutical R&D, particularly in basic pharmaceutical sciences, which Malva et al. (2015) define as "the systematic study directed towards greater knowledge or understanding of the fundamental

aspects of phenomena and observable facts without specific immediate commercial applications in mind" (p. 673). In the current review, we found a number of studies indicating that firms pursuing basic science research are more likely to generate radical drug innovations than those who do not (Jong and Slavova 2014; Malva et al. 2015; Sternitzke 2010). A potential mechanism for this finding may be that the buildup of internal basic scientific knowledge generates more absorptive capacity, which enables company scientists to identify, absorb, and integrate critical external knowledge, thereby increasing their likelihood of developing radical drug innovations (Belderbos et al. 2016). Belderbos et al. (2016) provide another possible explanation for why investments in basic science lead to more radical innovation: The more in-depth, in-house scientific expertise, the easier it is for firms to become engaged in top-tier collaborations with research universities. Thus, there is a link to the previously discussed managerial level of *external knowledge sourcing*.

However, Malva et al. (2015) observe that the positive relationship between basic science and radical innovation exists only if the basic science efforts are directed toward the understanding of *new* technology domains. Phene et al. (2006) further specify that new technologies that are very different from the absorbing company's current knowledge stock have an important impact on radical innovation only if the technology is sourced from the same geography, highlighting the difficulty of integrating new complex knowledge above a certain threshold.

While some research indicates that investments in basic pharmaceutical science are associated with the creation of radical drug innovation, the empirical findings of Watts and Hamilton (2013) point to the opposite: Firms investing more in *applied* science (i.e., drug development) outperform (in terms of their number of radical innovations) pharmaceutical companies focused more on basic science. Watts and Hamilton (2013) argue that firms oriented toward basic science may be at high risk of failure in terms of their commercial success, and suggest that these firms allocate more time and resources to product development and commercialization efforts.

Another approach for the creation of new knowledge that may eventually lead to radical innovations is described by Dunlap et al. (2014), who find that firms that source and build their new knowledge internally from in-firm international affiliates are more likely to deliver radical innovations than firms that source new knowledge only locally or from outside firms. International pharmaceutical companies set up and gain information from their international affiliates that tap into local knowledge through knowledge spillovers (Dunlap et al. 2014;

Gilsing and Nooteboom 2006). For this to happen, according to Dunlap et al. (2014), firms must be able to effectively share high-quality information across both local and global levels if they aim to successfully create radical innovations. However, as discussed above, Zucker et al. (2002) question the existence of knowledge spillovers, arguing that knowledge acquisition only occurs when scientists from different organizations actually work together (i.e., remunerated collaboration).

Other research (e.g., Dunlap-Hinkler et al. 2010; Karamanos 2012) reveals a positive relationship between the existing knowledge stock of a firm (measured through the number of previous radical innovations or patents associated with that firm) and the likelihood of new, additional radical innovations, emphasizing the benefits of knowledge accumulation and organizational learning over time (Arnold and Troyer 2016). Dunlap-Hinkler et al. (2010) note that the *types* of previous innovations play a role in determining future innovations. More specifically, they find that radical innovations are more beneficial than incremental innovations with regard to future radical innovations. They argue that radical innovation is associated with a higher level of organizational ambidexterity and absorptive capacity than incremental innovation, which "reduces the knowledge complexity and diversity within the firm, which dampens the need for effective communication and coordination, which is necessary for new learning and technological change" (Dunlap-Hinkler et al. 2010, p. 121). However, the empirical findings of Karamanos (2016), conversely, do not support a positive relationship between existing radical innovations and new ones.

3.6.2.3 R&D investments

Each year, pharmaceutical companies around the globe invest in excess of 100 billion U.S. dollars in R&D (Munos and Chin 2011). Findings from the current literature review suggest that pharmaceutical companies that invest more in R&D activities produce a higher number of radical drug innovations. For example, Dunlap et al. (2014) find that 1 per cent increases in R&D spending lead to .22 per cent increases in radical drug innovations. Researchers argue that R&D spending results in radical innovations because firms with higher R&D investment budgets can dedicate more resources to basic science research (discussed above), including in areas with very high R&D program failure rates (i.e., areas with high unmet medical needs) such as Alzheimer's disease (e.g., Arnold and Troyer 2016; Dunlap et al. 2014; Dunlap-Hinkler et al. 2010). Arnold and Troyer (2016) show that the relationship between R&D investments and radical drug innovation is likely moderated by top management leadership. They argue

that managers who are incentivized for long-term value creation take more risks, spend more on R&D, and see greater increases in radical innovations than managers who are negatively impacted by lack of short-term profits and, thus, are less willing to allocate resources for radical innovations.

However, as in the case of the previously discussed determinants, we found ambiguous and sometimes contradicting empirical results in our review. For example, on the one hand, Quintana-García and Benavides-Velasco (2011) as well as Wuyts et al. (2004) provide evidence that higher R&D investments lead to more radical and incremental innovations, not just radical innovations. On the other hand, Yeoh and Roth (1999) report that internal R&D investments have a direct *negative* effect on radical innovation because high internal R&D investments lead to the buildup of internal organizational routines that might impede a firm's ability to effectively tap into external knowledge.

3.6.2.4 Firm size

Sorescu et al. (2003) note that research on the relationship between firm size and innovation is the "second largest body of literature in industrial organization economics" (p. 82). While some argue that small pharmaceutical companies deliver more radical innovations than large ones (e.g., Dunlap-Hinkler et al. 2010; Kamuriwo et al. 2017; Malva et al. 2015), other studies come to the opposite conclusion that large firms are more likely to produce radical drug innovations (e.g., Fernald et al. 2017; Jong and Slavova 2014; Karamanos 2016; Quintana-García and Benavides-Velasco 2011; Sorescu et al. 2003). On the one hand, the arguments to support the claim that small firms deliver more radical innovations are centered around their nimbleness and lack of bureaucracy (Dunlap-Hinkler et al. 2010). Moreover, small firms might be more determined to succeed because the failure of a clinical program may end the existence of such companies. On the other hand, the arguments to support the claim that large firms deliver more radical innovations are positioned around economies of scale and scope, the ability to fund R&D extensively (Karamanos 2016), and the availability of slack resources to invest in the company's core activities such as basic science research (Ahuja and Lampert 2001; Sorescu et al. 2003). Yeoh and Roth (1999) find that large, more established firms benefit from their years of experience, their therapeutic differentiation, and their access to external knowledge. They also argue that these factors, rather than the firm's size itself, are responsible for greater radical innovations.

In line with the theoretical uncertainty regarding whether large or small firms are more likely to drive radical innovations, we also found conflicting empirical results. While some studies show a positive effect of firm size on radical, but not on incremental innovation (Dunlap-Hinkler et al. 2010; Fernald et al. 2017; Jong and Slavova 2014), other research presents evidence for a relationship between firm size and both radical and incremental innovations (Karamanos 2016; Quintana-García and Benavides-Velasco 2011). Yet others (Dunlap et al. 2014) find a positive relationship between firm size and incremental innovations. As such, it is not just unclear if small or large firms create more radical innovations, but also if firm size is a unique determinant of radical innovation at all.

3.6.3 Business Processes

The relationship between business processes and radical drug innovation was examined in 10 out of the 38 studies in this literature review. As mentioned in the *Background* section, an end-to-end innovation portfolio management process including stage-gates has been found to be critical for firms to be able to innovate. Malva et al. (2015) find that very focused project portfolios (i.e., where firms develop drugs that are based on a few select technology classes), which are characteristic of small biotechnology-focused firms, help them to deliver more radical drug innovations. This might be explained by the focus that such firms are able to maintain. Indeed, both Cammarano et al. (2017b) and Xu et al. (2013) argue that broad, diverse portfolios lead to a lack of R&D focus. However, large pharmaceutical firms tend to have sizable R&D portfolios with many drug candidates from very different disease areas (e.g., from Alzheimer's to oncology to ophthalmology). It is very easy for firms to lose focus when operating such complex portfolios.

Watts and Hamilton (2013) discuss a potential negative effect of portfolio management processes on radical drug innovation. Through portfolio management, firms allocate their resources to individual R&D projects based on assessed risks and returns. This process might lead to the elimination of riskier R&D projects to favor less risky ("safer") drug candidates. This risk avoidance can lead to lower numbers of radically innovative drugs and increased numbers of incrementally innovative ones.

None of the studies in this literature review discuss the actual process of portfolio management within firms (i.e., how the process actually works). However, we found several studies that examine the relationship between the portfolio management approach for a firm's external R&D collaborations and radical drug innovation. This means that the portfolio

management approach is analyzed in the unique context of pharmaceutical innovation, where external knowledge sourcing through R&D collaborations is of utmost importance for a firm's ability to develop radically innovative drugs. As firms enter into R&D collaborations over time, they need to actively manage their alliance portfolios. Research examined in this literature review shows a direct relationship between alliance portfolio structure (direct ties with many other organizations in a dense network) and radical drug innovation (e.g., Karamanos 2012, 2014; Wuyts et al. 2004).

3.7 Discussion and implications

Prior studies have advanced our general understanding of the firm-level determinants of radical innovation. It is well established that firm-level determinants of radical innovation are industry-specific (Pavitt 2005) and, as such, they need to be examined within a specific industry context (i.e., not generically). However, the results of this systematic literature review demonstrate that our understanding of firm-level determinants of *radical innovation in the pharmaceutical industry* is still emerging, which is evidenced by the low number of papers on this topic that we were able to identify. Taken together with the unique nature of the pharmaceutical industry in terms of costs, risks, and time frames, our current ability to explain and understand the determinants of radical drug innovation is incomplete. Given these limitations, we believe that a major contribution of this paper is to outline an *agenda for future research*, which we do next. We then discuss the managerial implications of the findings from this systematic literature review.

Previous literature on radical drug innovation has tended to focus de facto primarily on two firm-level determinants: *external knowledge sourcing* and *internal knowledge management*. External knowledge sourcing is particularly important for the first step of the pharmaceutical front-end innovation (FEI) process (i.e., idea generation through disease biology understanding) because most new knowledge is generated outside individual firms and, as such, it is critical for pharmaceutical firms to ensure effective access to relevant external knowledge. The other extensively examined determinant – internal knowledge management – is most frequently discussed in the context of building up absorptive capacity within a firm, which, in turn, enables external knowledge sourcing.

Findings from the current study emphasize that the ideation phase within the FEI process is important, but that much less is known about the significance of the other phases within the pharmaceutical FEI process (i.e., exploratory project discovery, drug discovery, and

preclinical tests) with regard to radical drug innovation. It is argued in the current literature of radical innovation that the entire FEI process – not just the ideating phase – differs for radical (as opposed to incremental) innovation (Aagaard and Gertsen 2011; Koen 2004). Therefore, research on the other FEI phases (in addition to ideation) and their impacts on radical drug innovation is needed.

The other two frequently discussed determinants of radical drug innovation – *R&D investments* and *firm size* – are often discussed in a way that suggests an over-simplified understanding of radical drug innovation. Findings based on the current literature review suggest that more granular / micro-level determinants associated with these factors likely play an important role in a firm's ability to deliver radical drug innovations. For example, research indicates that higher levels of R&D investments in pharmaceutical firms lead to higher outputs of radical drug innovations. Such research tends to treat the pharmaceutical innovation process basically as a black box. However, given the importance of the FEI process within the entire R&D process, we need a more nuanced understanding of the impacts on radical drug innovation of spending during the front-end process of pharmaceutical innovation (i.e., the research-related stages of the pharmaceutical R&D process) versus spending on clinical development (i.e., later stages of the R&D process). There is currently no empirical evidence to guide practitioners who wish to increase radical drug innovation on how much to spend on FEI / research versus development. Instead, there is only generic evidence to indicate that more should be invested in pharmaceutical R&D overall, which is not very informative or helpful in a practical sense. In addition, it is currently not clear whether firm size has a direct impact on radical drug innovation at all. Findings from this paper suggest that any impacts of firm size on radical drug innovation may be indirect, given that larger firms tend to have more resources to invest in R&D (our limited understanding of which we have just discussed). Thus, we question the value of additional macro-level research on these two determinants, and instead argue for more research on these determinants from a granular perspective.

In this paper, we have identified a relatively small number of studies that examine the *leadership* and / or the *culture* of a firm as a critical determinant of radical drug innovation. The low number of studies on this topic may be because these determinants are best assessed via research performed inside pharmaceutical firms, which can be challenging given the industry's need to protect their intellectual property and knowledge. We found empirical evidence that leadership is more important for the pharmaceutical FEI process than it is for the drug development-focused stage. However, this differentiation is not evidenced in the papers

that examine the relationship between a firm's culture and radical drug innovation. Instead, the impacts of firm culture on radical drug innovation tend to be examined more generically. It would be helpful to understand what kind of culture supports radical drug innovations during the FEI / research phases and what type of culture is most beneficial during the development phases. For example, at the (early) FEI phases, risk taking is incredibly important (because decisions are made regarding whether to advance drug candidates in the context of very limited information). However, risk taking is less of an issue during the later clinical development / testing phases, when the objective is to design and run clinical trials to assess safety and efficacy. These clinical trials are highly regulated and, as such, do not involve much risk taking. Future research should examine whether the same culture is needed in both the FEI / research and development stages in order to achieve radical drug innovation.

Pharmaceutical innovation is a process that involves turning *new knowledge* (resulting from a deep understanding of the disease biology) and *technological inventions* (e.g., monoclonal antibodies and CRISPR gene editing) into new drugs. It is well established that pharmaceutical technology evolves by quantum jumps (Achilladelis and Antonakis 2001) and that new technological breakthroughs can enable new classes of drugs. For example, Bakhrebah et al. (2018) describe how the CRISPR technology provides a new paradigm to target infectious disease pathogens. However, none of the 38 papers included in this review examine the extent to which new pharmaceutical technology enables radical drug innovation. We suggest that future research examine the relationship between major technological changes and radical drug innovation, particularly to understand the relative importance of new technologies when compared to other firm-level determinants of radical drug innovation.

A sharp contrast between the current state of research on firm-level determinants of radical innovation in general and research on firm-level determinants of radical *drug* innovation specifically is noticeable with regard to our understanding of the process character of innovation. We have three observations related to this point that should be addressed by future research. First, in the *Background* section of this paper, we discuss the evolution of our understanding of innovation from a simple / linear process to complex interactive models with multiple actors and sources. However, the pharmaceutical innovation process is primarily described as a linear process in most of the papers that we analyzed for this review. In addition, most papers do not examine interdependences between the various process steps (and their influencing determinants). As a consequence, research typically studies firm-level determinants of radical drug innovation in isolation, neglecting the process character. We see

an opportunity for future research to examine how the innovation *process* is effectively organized in pharmaceutical firms to facilitate radical drug innovation. In particular, it would be helpful to understand any differences in the process character between the FEI / research phases (where more process flexibility is needed) and the later clinical development phases (where less process flexibility is needed). Moreover, future research should provide additional insights into the interactions between the individual R&D process phases (as emphasized by the fourth-generation innovation models, which perceive the innovation process as running in parallel with feedback loops across various organizational functions). For example, it would be valuable to explore how evidence from clinical trials flows through feedback loops back to basic research, exploratory project discovery, and drug discovery organizations (see *Figure 8*), thereby effectively informing ongoing and future work on radical drug candidates.

Second, none of the 38 papers that we analyzed examine the established argument (in the literature on radical innovation in general) that stage-gate models, which are widely used in the pharmaceutical industry, potentially hinder radical drug innovation because of too much formality, hence reducing the flexibility needed to develop radical drug innovation. In this context, future research should contribute to a better understanding of how flexible stage-gate governance models (e.g., real-time decision-making instead of fixed governance cycles) support radical drug innovation. In addition, it would be valuable to examine strategies for driving a firm's research scientists / corporate managers toward a mindset of deprioritizing drug candidates for which there are better drug candidates available (e.g., through external R&D partnerships), even if those drug candidates meet all stage-gate criteria.

Third, research studies have paid very little attention to the impact on radical drug innovation of the current evolution of the pharmaceutical innovation process from a closed networked innovation model (fifth-generation model) to an open innovation model (sixth generation). Schuhmacher et al. (2013) report that many pharmaceutical firms are "leaving the more traditional R&D model and […] reforming pharmaceutical R&D in the direction of open innovation" (p. 1136) to increase their R&D productivity by sourcing more external drug candidates and reducing in-house research efforts (which is very costly). While this type of move reduces the overall R&D cost basis of a firm, it also importantly reduces a firm's absorptive capacity (Schuhmacher et al. 2013), which in turn might decrease the firm's ability to identify, source, and integrate external knowledge needed for radical drug innovation. Thus, future research should analyze the net benefits of open innovation on radical drug innovation.

In particular, we need a better understanding of the extent to which the higher leverage of external partnerships outweighs the reduced absorptive capacity of the focal firm over time.

This literature review also reveals that many of the empirical findings on this topic are contradictory, probably because the studies rely on different definitions and measures of radical drug innovation. Studies on radical drug innovation are plagued by ambiguous definitions (or no industry-specific definitions at all) and untested measures of the concept. Different measurement methods such as patent counts, NME counts, or joint counts of NME and FDA Priority Review classifications were used to measure radical drug innovation in this review's 38 papers, despite limited efforts to validate these measures, and to evaluate the differences and similarities between them. Innovation scholars seem to assume that radical drug innovation measures are validated because none of the 38 papers in this review discuss the validity of their radical drug innovation measures. Instead, many of the papers only cite previous papers that used the same measurement methods. Clearly, it is challenging to define and measure an innovation's radicalness because it is a theoretical concept. However, we argue that the use of patents to operationalize an innovation's radicalness, which is the most common measurement method, is not appropriate because patents are based on inventions, not innovations. Studies using patents typically assume a later successful commercialization of a patent (i.e., invention), but such an assumption is questionable because not all patents lead to commercial products.

Before we can expand our understanding of radical drug innovations and the determinants that are important for their development, a generally acceptable definition of, and validated measurement method for, this central concept is needed. Future research should address this need. In particular, studies should examine whether current measures of radical drug innovation actually assess what they purport to and should determine which of the dominant current measures (i.e., NME counts, joint counts of NME, and Priority Review designations) is the most valid. If research shows that none of the current measures are valid, then a new measurement method should be developed and validated.

In addition to providing an *agenda for future research* on firm-level determinants of radical drug innovation, there are several *managerial implications* that can be derived from this systematic literature review. Firms that take on the risk of investing in, and focusing on, the development of radically innovative drugs do so knowing that the failure rates for such an endeavor are high. Leaders and managers of these firms must do everything they can to set up their firms for success. As such, they would do well to inform themselves as much as possible about the determinants that are key for successful radical drug innovation. The results from the

current study offer guidance for leaders and managers within the pharmaceutical industry who are engaged in the development of radical drug innovations.

Successful radical drug innovations should be understood as a process outcome, often resulting from a combination of internal R&D knowledge and external knowledge sourcing. As such, pharmaceutical firms need to simultaneously build and sustain internal scientific knowledge, as well as identify and absorb new external knowledge. Because a significant amount of knowledge is created outside of individual firms – scientific advances are usually driven by research universities and pharmaceutical start-up firms – external knowledge sourcing through R&D collaborations is particularly important in this industry.

From the perspective of the absorbing firm, external knowledge can be best accessed through direct ties in the form of R&D alliances. In particular, firms that are able to access heterogenous external knowledge can avoid internal knowledge traps, thereby making it more likely that they will eventually develop radical drug innovations. The experience that a pharmaceutical firm has with managing R&D collaborations seems to positively impact the firm's ability to develop radical innovations, particularly when R&D alliances are repeated with the same partner (Wuyts et al. 2004). Firms engaged in R&D alliances should focus on managing the information asymmetry that often occurs across these relationships, thereby enabling better knowledge flow and increasing the chance of developing radical innovations. Interestingly, we also found that M&As (despite their frequent occurrence in the pharmaceutical industry) are not positively associated with radical drug innovation, so organizations should seriously consider their objectives when embarking upon this type of activity.

Before a firm can successfully engage in R&D collaborations with universities and other firms, it needs to possess the capacity to identify and absorb new, relevant external knowledge (i.e., absorptive capacity). To develop absorptive capacity, firms should focus on building up their internal scientific knowledge, which requires significant R&D investments over time. One way of doing this is by operating multiple R&D centers in different regional pharmaceutical clusters and tapping into diverse local knowledge bases, which increases internal scientific knowledge and, eventually, absorptive capacity. In addition, firms should pay attention to the type of knowledge they accumulate, as it will have an impact on their ability to develop radical drug innovations. A business model based on both incremental and radical drug innovations might be less promising in comparison to one that is entirely based on radical

drug innovations, assuming that the primary objective of the firm is to develop and commercialize radically innovative drugs.

Top leaders should be aware of the important role they play in developing effective radical drug innovations and should consider the specific types of characteristics that are particularly important for their type of firm. We found that the impact of top leaders varies by the type of pharmaceutical firm. For example, the educational background and professional experience of leaders as well as their previous experience in founding and developing pharmaceutical start-ups are particularly important for small, research-oriented pharmaceutical firms. Because these types of firms tend to have science-committed cultures with deep scientific knowledge, the educational background of their top leaders is critical because they need to be able to understand scientific context and to believe in the science pursued by their firms.

The role of leaders in large firms appears to be different than it is for leaders of small firms. Leaders of large firms do best in terms of radical innovation by focusing on the buildup of absorptive capacity, engagement in R&D collaborations, and maintenance of the infrastructure and global development needed to test the safety and effectiveness of promising drug candidates. Moreover, given the typical size of these more established firms, a culture of effective knowledge sharing between a company's divisions (particularly between a firm's research organization and development organization) is critical, which needs to be promoted and enabled by top leaders. Finally, when leaders in large firms emphasize behavior controls (e.g., centralization, formalization, or frequency of performance appraisals) and output controls (e.g., goal specificity; emphasis on output, rewards, and recognition), they support radical drug innovation by enabling scientists to focus on their work and to be productive in ways that align with company goals.

3.8 Conclusions and limitations

Pharmaceutical R&D is a risky, lengthy, and costly business. Most drug candidates never make it to market because of safety concerns and / or lack of effectiveness in treating their targeted clinical conditions. However, the few drugs that do make it to market receive patent protection for a limited period of time, helping the innovating company recoup its investment and make profits. Pharmaceutical firms can minimize their financial risks by developing less risky new drugs with already validated targets and mechanisms of action. However, this approach typically leads to incremental drug innovations with little to no additional therapeutic value

over already existing drugs. Because an increasing number of healthcare payers will only pay a premium for radically innovative (i.e., clinically differentiated) drugs, pharmaceutical firms are financially incentivized to develop radical drug innovations over incremental ones. Firms that pursue the development of radically innovative drugs should have a comprehensive understanding of the firm-level success factors of radical drug innovation.

The objective of this systematic literature review was to map, in a transparent and reproducible manner, existing knowledge in the literature on firm-level determinants of radical drug innovation. More than 4,100 peer-reviewed journal articles and PhD theses were considered, and 38 were included in the narrative synthesis. Following the classification suggested by Crossan and Apaydin (2010), we grouped the various determinants of radical drug innovation into three distinct categories: leadership, managerial levers, and business processes. Within these categories, we found the following firm-level determinants to be particularly important for radical drug innovation:

- External knowledge sourcing (managerial lever);
- Internal knowledge management (managerial lever);
- Ability of top leaders to innovate, which is determined by their educational background and professional experience (leadership); and
- Firm leaders' focus on shaping innovation and performance cultures (leadership).

However, findings from this literature review also reveal that our ability to explain and understand the firm-level determinants of radical drug innovation is currently limited, as evidenced by the low number of identified papers in this systematic literature review. Although most pharmaceutical firms have similar organizational setups (e.g., R&D organizations are functionally organized in very similar ways) and processes (e.g., stage-gates with almost identical stages; Aagaard and Gertsen 2011), their outcomes in terms of radical drug innovation vary importantly. In this paper, we have identified some important differentiating determinants. However, these determinants are not comprehensive enough to provide a full understanding of how radical innovations are achieved within pharmaceutical firms. Previous research has typically examined firm-level determinants of radical drug innovation in isolation and has failed to consider process character, which we believe is critical for understanding radical drug innovation.

We would like to address some of the limitations associated with the methodology used for this systematic literature review. First, systematic literature reviews emphasize the technical aspects of papers more than the conclusions and interpretations (Bryman and Bell 2015). As

such, our screening process was focused on ensuring that the selected papers had clear research designs, well-described and rigorous methodologies, and reasonable assumptions. Therefore, we may have screened out studies that were properly executed and had interesting empirical findings, but the technical aspects of the research were not well documented. Another potential limitation associated with systematic literature reviews is that the synthesis process is quite inductive and interpretive (i.e., prone to bias of the researcher; Thorpe et al. 2005). To limit this subjectivity, a second researcher conducted the synthesis in parallel with the first to compare the findings. However, researcher biases may still play a role here. This type of work might also be limited as a result of publication bias (i.e., the idea that positive results are more likely to be published than negative ones; Kitchenham 2004; van Witteloostuijn 2016). Finally, the initial screening of identified papers was performed based only on the titles and abstracts of each paper. While this method was practical given the high number of identified papers, it may have led to the exclusion of potentially relevant papers.

One of the major contributions of this paper has been to provide an agenda for future research. However, before research can address the topics that we outlined above and expand our understanding of radical drug innovation and the determinants that are important for its development, a generally acceptable definition of, and validated measurement method for, this central concept is needed. As Bamberger (2017) reminds us, "after all, no matter how interesting a phenomenon may be, until it can be accurately and reliably measured, our ability as scholars to understand such phenomena, explain their origins and demonstrate their implications for management is extremely limited" (p. 237). This should indeed be a primary focus of future research on radical innovation within the pharmaceutical industry.

Chapter 4 | Study 3

Towards a more in-depth understanding of firm-level determinants of radical drug innovations: Semi-structured expert interviews

4.1 Abstract

Radical drug innovations are of great importance to pharmaceutical firms and public health. Understanding the determinants involved in successful radical drug innovations is key to increasing their output. Research to date has not provided a solid understanding of why some firms succeed in developing radical drug innovations, nor has it offered conclusive evidence about which determinants are critical for the successful development of radical drug innovations. The current literature focuses primarily on four determinants of radical drug innovation: *access to external knowledge*, *internal knowledge management*, *firm size*, and *R&D investments*. However, findings from the current expert interview study emphasize that the culture of pharmaceutical companies, which is rooted in *following the science* and *risk-taking, learning from mistakes,* and *accepting failure*, as well as *focused, constrained and milestone-driven funding of research and development* are paramount for radical drug innovations. In addition, we add to the current literature on defining radical drug innovations. Despite the definitional ambiguity found in the current literature, radical drug innovation is unambiguously defined by the participants of this study through their novelty and therapeutic benefit (i.e., impact) when compared to already existing drugs. Moreover, drug novelty is not always a necessary condition to define a radically innovative drug, while additional therapeutic benefit is always a criterion.

4.2 Introduction

Engaging in the business of pharmaceutical innovation (i.e., drug innovation) is costly, lengthy, and risky. It costs up to 1.8 billion U.S. dollars to discover and develop a new drug (Mestre-Ferrandiz et al. 2012). These investments are often necessarily high because pharmaceutical research and development (R&D) cycles are long and associated with high attrition rates (which necessitate more funding). It takes, on average, between 12 and 14 years to bring a new drug to market because of the rigorous testing process a drug must go through to become commercialized (Schuhmacher et al. 2016; Sternitzke 2010; Van Norman 2016). Moreover, drug innovation is risky because most R&D programs in pursuit of new drugs fail. The overall success rates of pharmaceutical R&D are very low. On average, only five per cent of drug candidates entering clinical development make it to market (Adams and Brantner 2006; Munos and Chin 2011).

Moreover, even when they do make it to market, not all new drugs are equal in terms of the additional therapeutic benefit they provide over already existing drugs. For example,

Régnier (2013) reports that 58 per cent of the 431 new pharmaceutical drugs approved by the U.S. Food and Drug Administration (FDA) between 1990 and 2004 offered no significant therapeutic improvements in comparison to drugs that had been already on the market at the time of the approvals. Similarly, and more recently, Wieseler et al. (2019) report in the *British Medical Journal* that more than 50 per cent of newly approved drugs did not offer additional therapeutic benefit when compared to already existing drugs.

This is particularly notable because healthcare payers in an increasing number of countries are generally less willing to fund new drugs with undifferentiated therapeutic benefits. Instead, they increasingly focus their funding on news drugs that improve patient health and address unmet medical needs in ways that were not previously achievable (Stiller et al. 2020). We will refer to these drugs as *radical drug innovations*, which have the potential to extend life (despite life-threatening clinical conditions), cure life-threatening clinical conditions, and / or address previously unmet medical needs by offering effective treatments for medical conditions (e.g., rare diseases such as hemophilia) for the first time. This is different from incremental drug innovation, which is defined here as a pharmaceutical drug that improves an existing drug beyond its primary indication and / or enhances other drug properties such as drug administration options. These drugs offer limited clinical benefits over existing ones.

Radical drug innovations are of great importance to pharmaceutical firms and public health. Understanding the determinants involved in successful radical drug innovations is key to increasing this type of output in the future. However, in their recent systematic literature review of the firm-level determinants of radical drug innovation, Stiller et al. (2021) conclude that our ability to explain and understand the firm-level determinants of radical drug innovation is currently limited for the following three reasons. First, there is currently only scarce empirical evidence available (i.e., there is a low number of studies that examine the firm-level determinants of radical drug innovation). Second, current research on the topic mainly focuses on *external knowledge sourcing*, *internal knowledge management, firm size,* and *R&D investments*, but much less is known about the relationship between other important firm-level determinants of radical innovation that are not specific to the pharmaceutical industry – such as *culture* and *leadership* – and radical drug innovations. Third, current research on determinants such as *R&D investments* and *firm size* tends to treat the pharmaceutical innovation process basically as a black box, particularly the early innovation phases (frequently referred to as the fuzzy front-end innovation (FEI) process), during which opportunities are

identified and initially assessed (Aagaard 2012; Gassmann and Schweitzer 2014; Hakkarainen and Talonen 2014). It is argued that the FEI process is particularly critical for radical innovations (as opposed to incremental ones; Aagaard 2012, 2015; Rice et al. 2001) because the ideas needed for radical innovations are formulated during the fuzzy front-end phase (Nicholas 2014). Consequently, many believe that the FEI process for radical innovations needs to be managed differently than FEI used for incremental innovations (Aagaard and Gertsen 2011; Koen 2004; Reid and De Brentani 2004). However, according to Gassmann and Schweitzer (2014), "the front end is poorly understood, and managers experience a lack of knowledge on how to best organize the front end" (p. vi).

The current paper has a two-fold objective: (1) to add empirical evidence to the currently limited understanding of firm-level determinants of radical drug innovation, and (2) to provide a more granular understanding of firm-level determinants of radical drug innovation through semi-structured interviews with pharmaceutical R&D experts. This research is guided by the following research question: *How do key firm-level determinants influence the development of radically innovative drugs, particularly with regard to the front-end innovation process?* The *Background* section discusses the current understanding of firm-level determinants of radical innovation in the literature, particularly with regard to radical innovations within the pharmaceutical industry. The *Methodology and analysis* section provides details about the methodology, sample, and analysis. The *Results* section presents the study findings, and the *Discussion* section includes a discussion of the results and directions for future work. Lastly, overall *Conclusions* about the current research are presented.

4.3 Background

The current understanding of firm-level determinants of radical innovation in general (i.e., those that apply to settings both inside and outside the pharmaceutical industry) will first be briefly discussed before detailing the current, and less complete, understanding of firm-level determinants of radical *drug* innovation (i.e., within the pharmaceutical industry).

4.3.1 Radical innovations

Radical innovation has been defined in many different ways in the literature (Green et al. 1995; Kotsemir and Meissner 2013; Kovacs et al. 2019; McDermott and O'Connor 2002). While some scholars define radical innovations entirely through a high degree of newness, others conceptualize radical innovations by both a high degree of newness and impact (Kovacs et al.

2019). Innovation can be conceptualized as a process to transform an "idea or invention into a product, or into something that has an economic impact" (Hakkarainen and Talonen 2014, p. 63). This process can be organized and carried out in various ways across different industries, firms, teams, leaders, and managers. Research indicates that how this process is organized and carried out plays a critical role in the firm's ability to develop (radically) innovative outputs (Kahn 2018). Moreover, it is well established that the accumulation of knowledge within a firm (e.g., Zhou and Li 2012), the corporate culture of a firm (e.g., Tellis et al. 2009), and collaborations within a firm (e.g., Koberg et al. 2003) are important determinants of radical innovation.

Researchers also note that the early phases of the innovation process (i.e., the front-end innovation process; FEI) are critical for the development of radical innovation because it is during the FEI process that initial ideas that may lead to radical innovations are developed (Aagaard 2012, 2015; Nicholas 2014; Rice et al. 2001). This is not the case for incremental innovations. As such, some argue that the early phases of the innovation process should be managed in ways that differ from the management of later phases of the process (Aagaard 2012; Gassmann and Schweitzer 2014; Hakkarainen and Talonen 2014) and that the FEI process should be managed differently for radical versus incremental innovations (Aagaard and Gertsen 2011; Koen 2004; Reid and De Brentani 2004). Although the theoretical discussion of the relationship between the FEI process and radical innovations has advanced in recent years, there is still very limited empirical evidence to support theoretical arguments about what differentiates the FEI process for radical and incremental innovations.

The variations in how radical innovation is defined have resulted in the utilization of varying approaches for measuring the concept. It is important to recognize that the use of different measurement approaches makes it difficult to study and accurately understand radical innovation, inhibiting the comparison of empirical results reported in the literature.

4.3.2 Radical drug innovations

As is the case with radical innovation in general, radical innovation within the pharmaceutical industry (i.e., radical drug innovation) is associated with different definitions (de Solà-Morales et al. 2018; Morgan et al. 2008; Stiller et al. 2020). For example, a literature review found that 25 different definitions of drug innovation were presented in 36 academic articles on the topic (de Solà-Morales et al. 2018). The most common definitions focus on drug novelty, therapeutic benefits, or unmet medical needs addressed by a drug. These radical drug innovation

definitions tend to be either one-dimensional (e.g., drug novelty) or two-dimensional (e.g., drug novelty and therapeutic benefit – i.e., impact). Following Stiller et al. (2020) and Morgan et al. (2008), radical drug innovation is best categorized two-dimensionally, capturing both the newness and the therapeutic impact of a new drug because "in addition to being novel, drugs also need to be useful, in that they provide some additional therapeutic value (net of treatment risks) when compared with already existing drugs" (Stiller et al. 2020, p. 7). As such, for the current research study, we follow the two-dimensional conceptualization of radical drug innovation, which includes newness and therapeutic impact when assessing a new drug. Previous literature on radical drug innovation has – de facto – primarily focused on the following four firm-level determinants: *external knowledge sourcing, internal knowledge management*, *R&D investments,* and *firm size* (Stiller et al. 2021). Each of these determinants is discussed in greater detail below.

External knowledge sourcing is particularly important for the first step of the pharmaceutical FEI process, which involves the generation of new ideas through greater understanding of disease biology. External knowledge sourcing is important during this phase because the type of knowledge required for new idea generation is typically created by external organizations (Fosfuri and Tribo 2008). More specifically, scientific advances tend to be initiated by research universities as well as by pharmaceutical and biotechnological start-up firms that are dedicated to basic science (Achilladelis 1993; Zucker et al. 2002). Pharmaceutical firms, particularly larger ones, that hope to develop radical drug innovations are more likely to succeed if they have access to the type of transformational knowledge that characteristically exists in research universities and start-up firms (Cammarano et al. 2017b; Kamuriwo et al. 2017; Phene et al. 2006). Therefore, firms that effectively identify, acquire, and integrate external knowledge are more likely to develop radical drug innovations than those that do not. Firms with high absorptive capacity are better equipped to access the external knowledge they need to develop radical drug innovations.

The second firm-level determinant – *internal knowledge management* – is critical for building up absorptive capacity within a firm, which, in turn, enables external knowledge sourcing. There are various approaches for pharmaceutical firms that aim to develop internal knowledge that will advance them in their radical drug innovation efforts. One strategy is to invest in pharmaceutical R&D, especially basic pharmaceutical sciences, which Malva et al. (2015) define as "the systematic study directed towards greater knowledge or understanding of the fundamental aspects of phenomena and observable facts without specific immediate

commercial applications in mind" (p. 673). Indeed, studies show that radical drug innovations are more likely to come from firms that pursue basic science research than from those that do not (Jong and Slavova 2014; Malva et al. 2015; Sternitzke 2010). One reason for this finding may be that firms with high levels of internal basic scientific knowledge also have more absorptive capacity, which increases their likelihood of developing radical drug innovations through the identification, absorption, and integration of external knowledge (Belderbos et al. 2016). A focus on basic science research might also lead to radical innovations through increased collaborations with top-tier research universities, which may be easier to establish for firms that engage in basic science research (Belderbos et al. 2016). However, some research indicates that firms focused on applied science (i.e., drug development) are more likely to develop radical drug innovations than are firms that invest more in basic science (e.g., Watts and Hamilton 2013).

The final two most commonly discussed determinants of radical drug innovation are *R&D investments* and *firm size*. However, discussion of these determinants in the literature suggests a somewhat limited understanding of the nuances involved with these factors. We argue that the role of these determinants in the development of radical innovation is quite complex. For example, studies show that high outputs of radical drug innovation tend to be associated with firms that invest heavily in R&D (e.g., Arnold and Troyer 2016; Dunlap et al. 2014; Quintana-García and Benavides-Velasco 2011). However, these types of studies often do not provide much detail with regard to the nature, timing, and distribution of the R&D investments. We only know that greater investment in pharmaceutical R&D overall is valuable, which is not very informative or helpful in a practical sense. Instead, we need to better understand the impacts of specific types and timing of R&D spending on radical innovation (e.g., R&D spending during the front-end process of pharmaceutical innovation – i.e., the research-related stages of the pharmaceutical R&D process – versus spending on clinical development – i.e., the later stages of the R&D process). Leaders in decision-making positions would benefit from empirical evidence regarding how much to spend on FEI / research versus development.

Research on this topic has also resulted in ambiguous and sometimes contradicting results regarding the impact of R&D spending on radical and incremental innovations. For example, some studies have shown that higher R&D investments lead to more of both types of innovations (Quintana-García and Benavides-Velasco 2011; Wuyts et al. 2004). However, Yeoh and Roth (1999) argue that R&D investments actually have a direct negative relationship

with radical innovations. Again, more research is needed to help clarify these relationships of interest. In addition, some research posits that small pharmaceutical companies are more successful than large firms when it comes to delivering radical innovations (e.g., Dunlap-Hinkler et al. 2010; Kamuriwo et al. 2017; Malva et al. 2015). However, other studies have shown the opposite finding: that large firms are actually more likely than small ones to produce radical drug innovations (e.g., Fernald et al. 2017; Jong and Slavova 2014; Karamanos 2016; Quintana-García and Benavides-Velasco 2011; Sorescu et al. 2003). As such, it is not clear at this point whether *firm size* plays a role in the development of radical innovations. If we do find that firm size is related to radical drug innovation, additional research is needed to better understand whether the relationship is direct or indirect, given that larger firms tend to have more R&D resources, which may indirectly impact radical drug innovation.

The four determinants of radical innovation that we have just mentioned represent those that have been most commonly discussed in the literature (Stiller et al. 2021). However, much less is known about the roles that other firm-level determinants (which are not specific to the pharmaceutical industry) such as *leadership* and / or *firm culture* play in the radical drug innovation process (Stiller et al. 2021). Lack of research in these areas may stem from the fact that these determinants are most adequately measured by data collection within pharmaceutical firms, which can be challenging given the industry's need to protect intellectual property and knowledge. The research of Aagaard and Gertsen (2011), through an exploratory case study of a global pharmaceutical firm (headquartered in Denmark), is among the very limited number of papers that examine determinants of radical pharmaceutical front-end innovation. Through this work, Aagaard and Gertsen (2011) identified 11 key determinants (and importance scores) of radical pharmaceutical front-end innovation (see *Table 15*).

Table 15 – Key determinants of radical pharmaceutical front-end innovation process (Aagaard and Gertsen 2011)

Determinant	**Score**
Explorative team culture tolerant of failure	56
Efficient cross functional and cross disciplinary knowledge sharing and	55
Empowerment of employees to learn and explore	47
Innovation leadership motivating discussions of ideas	40
Clear communication of direction, status and goals	37
An innovation strategy & objectives guiding not dictating innovation	36
Targeted knowledge sharing and collaboration with external partners	32
Organizational structures supporting learning and knowledge sharing	30
FEI as a flexible learning process	27
Aligned, trained and easy-to-use IT systems and networks	20
Measures and measurement of innovation	20

Most of the key determinants (with high scores) identified by Aagaard and Gertsen (2011) relate to either the culture, knowledge (sourcing, accumulation, and sharing), and / or leadership associated with a pharmaceutical firm. As such, their findings emphasize the need for more research beyond the four determinants that have been most commonly studied up to this point (i.e., *external knowledge sourcing, internal knowledge management*, *firm size*, and *R&D investments*).

In conclusion, research to date has not provided a solid understanding of why some firms succeed in developing radical drug innovations, while others do not, nor has it offered any conclusive evidence about which factors are critical for the successful development of radical drug innovations versus incremental ones (Stiller et al. 2021). It is known that all drug candidates go through similar R&D processes within a firm, regardless of whether the drug candidate might turn out to be radical or incremental. We also know that the R&D process is set up and implemented relatively similarly across most pharmaceutical firms (Aagaard and Gertsen 2011). It follows, then, that the organization and execution – at a macro level – of a pharmaceutical firm's R&D process does not seem to be a distinguishing criterion for radical innovation output. So, a more nuanced understanding of firm-level determinants of radical drug innovation is needed. This type of nuanced understanding, particularly for the culture and leadership of a firm, can best be generated from inside of firms (e.g., through research methods such as interviews with subject matter experts).

4.4 Methodology and analysis

To appropriately address this study's research question and in response to the need for more research from within pharmaceutical firms (i.e., through the perspectives of subject matter experts), a qualitative research approach in the form of semi-structured interviews was chosen for this work. The objective is to provide a more nuanced and in-depth understanding of the relationships between firm-level determinants and radical drug innovation.

4.4.1 Semi-structured interviews

Interviews are a well-established method for the collection of research data, particularly in exploratory studies eliciting expert information and experiences (Harrell and Bradley 2009; Lewis 2003). According to DiCicco-Bloom and Crabtree (2006), semi-structured interviews are the most frequently used interview technique in qualitative research. Semi-structured interviews, as opposed to structured interviews (i.e., all questions planned in advance; all

interviewees asked the same questions in the same order) or unstructured interviews (i.e., no interview questions prepared in advance), were chosen because semi-structured interviews are based on a few predetermined questions with the opportunity to further explore topics depending on the information provided by the interviewees. As noted by Adams (2015), the "dialogue can meander around the topics on the agenda — rather than adhering slavishly to verbatim questions as in a standardized survey—and may delve into totally unforeseen issues" (p. 493). As such, semi-structured interviews allow the researcher to balance induction with structure through the combined use of predetermined questions and follow-up / exploratory questions. This, however, requires that the interviewer is sufficiently knowledgeable about the relevant topics, which is the case in this study because the author is an industry-insider. Despite some disadvantages associated with semi-structured interviews (e.g., they can be time-consuming; they require interviewer knowledge; Adams 2015), they are appropriate to address this study's research question, given that we do have insights from the literature to be 'tested' (the deductive, structured part), but recognize that these insights are incomplete, leaving many issues to be explored further (the inductive, unstructured part).

Because a rigorous data collection process significantly influences the quality and results of a study (Gibbs et al. 2007), an interview guide (see Appendix) was developed to facilitate the interviews. A total of 14 open-ended questions were prepared to elicit the interviewees' insights on the definition and measurement of radical drug innovation, as well as their understanding of which firm-level determinants of radical drug innovation are particularly critical. The interviewer had the flexibility to move the conversation in any direction of interest during the interviews. A pilot interview with one interviewee was conducted to test the interview approach and interview questions. After the pilot interview, some minor adjustments were applied to the interview guide (e.g., additional context was added to some questions to make them less ambiguous).

Because of the COVID-19 pandemic, all interviews were scheduled and conducted online. Upon request from some participants, the interview questions were sent to all participants prior to their interview. At the beginning of each interview, all interviewees were asked for their consent to record the interview. All interviewees gave their consent, and all interviews were then recorded. The average interview duration was approximately 45 minutes, which is in line with the recommendation made by Adams (2015) that semi-structured interviews should not exceed one hour, to minimize fatigue for both the interviewer and the interviewees. All interviews were then transcribed verbatim and analyzed according to the

analysis process described below. To maintain confidentiality, the interviewees' names were replaced with a numeric identifier in the interview transcriptions.

4.4.2 Participants

Participants for this study are R&D experts from various pharmaceutical companies, university research hospitals, and venture capital firms (that invest in pharmaceutical firms) in the U.S. and Europe, which represent two regions with large clusters of pharmaceutical firms that are heavily focused on R&D. We focused on getting access to R&D experts with extensive leadership experience in some of the world's largest pharmaceutical firms before moving to different senior leadership roles in smaller pharmaceutical firms (start-ups), venture capital firms investing in the pharmaceutical industry, and research universities. This approach allowed us to gain a variety of perspectives from representatives of different sized organizations of different types that play distinct roles in the radical drug innovation process.

The following inclusion criteria were used to determine eligibility for individual participation in this study:

- Pharmaceutical R&D expert overseeing a pharmaceutical firm's R&D organization;
- CEO or Chief Operating Officer (COO) of a pharmaceutical firm (including start-ups);
- Pharmaceutical R&D expert at a university hospital with extensive prior work experience in pharmaceutical firms; or
- Senior executive of a venture fund (with extensive prior work experience in pharmaceutical firms) that invests in pharmaceutical and / or biotechnology start-ups.

As alluded to above, given the need to protect intellectual property in the pharmaceutical industry, it can be challenging to get access to relevant / knowledgeable informants from within pharmaceutical firms. This situation influenced the sampling approach used in the current study. The author of this study relied on his professional network extensively to get access to firms and interviewees. A priori purposive and convenience sampling of firms were applied to identify and then to select interviewees based on their potential ability to contribute to the research, particularly through their expert judgements. Purposive sampling is a frequently used technique in qualitative research to identify and select informants that are knowledgeable about the study's topic of interest (Palinkas et al. 2015). Each informant is selected because of his / her ability to provide valuable information for the study (Etikan et al. 2016). In convenience sampling, practical criteria are relevant for the selection of informants (e.g., easy accessibility and / or availability, willingness to participate

in the study; Etikan et al. 2016). Both purposive and convenience sampling are non-probability sampling techniques. As a consequence of this sampling approach, this study's findings will be inferential rather than strongly generalizable findings, which would require random sampling (Harrell and Bradley 2009).

From the professional network, 15 potential candidates were contacted and expressed interest in the project. Four of these individuals did not ultimately find the time to get involved, and one candidate (a partner of a venture capital firm that invests in pharmaceutical companies) was excluded because the candidate had no previous experience working in a pharmaceutical firm. This resulted in a final sample size of ten, which was sufficient because no materially new information emerged after the seventh interview (i.e., data saturation was achieved, making it appropriate to stop the data collection; Gibbs et al. 2007).

The data for this research was collected through ten semi-structured interviews from seven pharmaceutical companies, two venture funds, and one university research hospital in the U.S., the UK, Switzerland, and Germany. Participants from different countries were selected to reduce potential cultural biases. *Table 16* shows the positions and educational backgrounds of each interviewee, as well as the type and physical location (country) of the firms where they work. One interviewee is female, and 9 interviewees are male. All interviews were conducted in June 2020.

Table 16 – Interviewees

Participant	Position & Academic Degree	Type of Firm	Country
1	CEO, PhD	Pharmaceutical or biotech start-up*	Switzerland
2	President	Pharmaceutical or biotech start-up*	U.S.
3	Co-Founder and CEO, Professor	Pharmaceutical or biotech start-up*	Germany
4	VP R&D, PhD	Pharmaceutical or biotech start-up*	U.S.
5	Disease Program Leader, PhD	Pharmaceutical or biotech start-up*	U.S.
6	Director, PhD	Research university hospital*	Switzerland

7	CEO, PhD	Pharmaceutical or biotech start-up*	U.S.
8	SVP R&D, PhD	Large pharmaceutical firm	UK
9	Partner, MD	Venture fund*	U.S.
10	COO & CFO	Venture fund*	U.S.

* with extensive prior work experience in large pharmaceutical firm(s)

4.4.3 Data analysis and coding

There is a wide choice of methods that can be applied for the analysis of qualitative research data. King's (2016) *template analysis* approach was chosen to analyze and interpret the transcribed interviews since it is more flexible than alternative methods such as *grounded theory* (which is very prescriptive) and less time consuming than *interpretative phenomenological analysis* (IPA). King (2016) defines template analysis as follows:

> Template analysis involves the development of a coding 'template', which summarises themes identified by the researcher(s) as important in a data set, and organises them in a meaningful and useful manner. (para. 2)

The major steps of template analysis are shown in *Figure 13*.

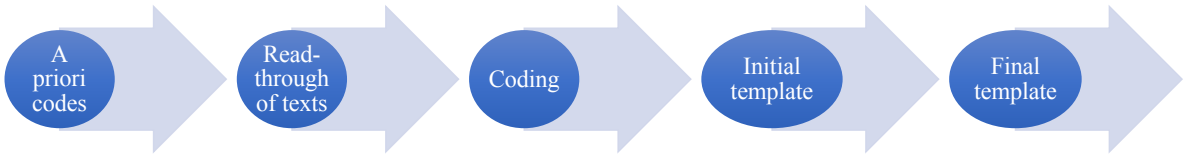

Figure 13 – Major steps of template analysis

For the initial coding of the transcribed interviews, a priori codes of firm-level determinants of radical drug innovation identified in the recent systematic literature review by Stiller (2019) were used. New codes emerged from the interview transcripts and were added to the template used for the current study, existing codes were modified based on the interview transcripts, and a priori codes that were not linked to any interview data were deleted. Two researchers coded the transcribed interviews separately and differences were discussed to align on common solutions. This quality check approach potentially increases the level of credibility, transferability, confirmability, dependability, and authenticity of the analysis results (Bryman and Bell 2015). After the initial coding of the transcribed interviews, the two researchers grouped and hierarchically structured the identified themes based on the research question.

From this process, we developed an initial template with broad themes and detailed sub-themes. The initial template was further developed by applying it to each transcribed interview. In cases where the template did not cover all themes in a transcript, the template was modified. As a consequence, the modified template needed to then be applied to all other transcripts. This iterative process continued until the template covered all relevant themes in all interview transcripts.

4.5 Results

Table 17 outlines all themes and sub-themes that emerged during the analysis of the data from the ten semi-structured expert interviews. To indicate the importance of the theme / sub-theme, *Table 17* also outlines how many of the ten participants discussed each theme / sub-theme, and how many times each theme / sub-theme was discussed across all interviews.

Table 17 – Themes and sub-themes regarding radical drug innovation

Theme	**How Many Participants Discussed It**	**How Many Times It Was Discussed Across All Interviews**
Definitions		
Radical drug innovations are defined through therapeutic benefit (i.e., impact) *and* novelty	8	N/A
Radical drug innovations are defined through novelty only	1	N/A
Radical drug innovations are defined through therapeutic benefit only	1	N/A
Therapeutic benefit (impact)		N/A
- Targets a previously undruggable target	*5*	*N/A*
- Addresses unmet medical need	*2*	*N/A*
Novelty		N/A
- *First-in-class*	*6*	*N/A*
- *New (manufacturing) technology*	*4*	*N/A*

Theme	How Many Participants Discussed It	How Many Times It Was Discussed Across All Interviews
Determinants of radical drug innovation output of a firm		
Company culture rooted in following the science	10	70
Culture of risk-taking, learning from mistakes, and accepting failure	9	63
Leadership and decision-making	10	53
Firm size	10	53
External knowledge sourcing	9	33
R&D investments	10	29

4.5.1 Definitions

Given the ambiguity regarding the definition of what exactly constitutes radical drug innovation (discussed in the *Background* section), all participants were first asked to define, according to their personal understanding, the concept of a radically innovative drug and how it differs from an incrementally innovative drug. The definition that a participant provided guided the subsequent discussion, in that interview, of firm-level determinants of radical drug innovation. In addition, this information allowed the interviewer to gauge the magnitude of alignment across the definitions provided by the ten experts.

As shown in *Table 17*, the definitions of radical drug innovation described by eight of the ten participants relied on a drug's level of novelty *and* impact (in the form of additional therapeutic benefit). At first glance, Participant 5 differed from most other participants because Participant 5 defined radical drug innovation primarily through novelty. According to Participant 5, the impact (i.e., the additional therapeutic benefit) of a new drug candidate is equally important, but only becomes evident after a long time (i.e., once the drug passes through late-stage clinical development and / or gets introduced onto the market). So, conceptually, Participant 5 also agrees with a two-dimensional definition of radical drug innovation (i.e., through novelty and impact), but expressed concerns about the measurement

of the impact. Only one participant – Participant 6 – conceptualized radical drug innovation one-dimensionally, through the additional therapeutic benefit of the drug (i.e., impact).

Interestingly, when participants were asked to provide specific examples of radically innovative drugs, Participants 2, 3, and 6 mentioned the drug Sovaldi® – a drug marketed by the pharmaceutical firm Gilead to treat hepatitis C. However, as pointed out by Participant 3, Sovaldi® is not a novel drug:

> *So, for example, another drug that has really changed the disease or has basically led to the disappearance of a disease is the Gilead hepatitis C drug, and this is not a first-in-class compound. There were others before, and yet this was the first that was really so effective that, basically, hepatitis C is about to disappear completely. (Participant 3)*

While this is the only deviating case that emerged during the interviews, it still highlights that drug novelty is not always a necessary condition to define a radically innovative drug. However, additional therapeutic benefit is always a criterion needed to categorize a drug as radically innovative. This conclusion was also explicitly mentioned by Participant 4: "And if you think about it, in my personal view, what is the most important criteria to characterize a drug as truly impactful, and that is always the impact to patients' quality of life."

The novelty of a radically innovative drug was defined by most participants (6/10) through the concept of being first-in-class. First-in-class drugs are those that offer a new and unique mechanism of action for treating a medical condition (Lexchin 2016). In this context, Participant 4 explained that

> *a radically innovative drug would probably target an undruggable target, so whatever was – at the time, or as a gold standard – not considered to be a druggable target, and all of a sudden, there is a new insight. There is some new science. There's new research that supports the idea that it actually can be targeted.*

Four participants defined the novelty of a radically innovative drug mainly through how its underlying technology is used. In this context, three recent examples of new technologies enabling the development of radically innovative drugs were mentioned:

a) the CAR-T technology to engineer patients' immune cells to treat their cancers (Participant 7);
b) the CRISPR gene editing technology (Participant 10); and
c) the Transport Vehicle (TV) technology to transport therapeutic proteins across the blood-brain barrier, which protects the brain from toxins (Participants 5 and 10).

One participant – Participant 2 – indicated that for a drug to be considered novel (and potentially radically innovative), the impact of the new technology must be so significant that it disrupts the entire pharmaceutical industry:

> *And so, I guess my first reaction to it is innovation, at least to disrupt the industry. Thinking about it just on, "How innovative is the drug?" to me is a little bit of the wrong question. To me, it's like, "How are you thinking in a completely different way about getting medicines to patients?"*

Half of the participants (5/10) defined the therapeutic benefit of a drug mainly through its impact on patients. This impact was further specified by some participants as clinically important improvements versus existing drugs (i.e., the current standard of care). Two participants went further to define the therapeutic benefit of radically innovative drugs through their ability to address unmet medical needs.

4.5.2 Determinants of radical drug innovation output of a firm

4.5.2.1 Company culture rooted in following the science

"Few other industries are as driven by science, research and development as the pharmaceutical industry" (Gassmann and Reepmeyer 2005, p. 233). Aligned with this belief, *following the science* is the firm-level determinant of radical drug innovation that was most frequently discussed among all ten participants. Both Participants 3 and 9 referred to the U.S. pharmaceutical firm Merck in this context. Participant 9 noted:

> *So, the culture and conviction at Merck at the time was very supportive. And I would say the culture at Merck early on and even in the 1950s and 1960s from George Merck – one of the founders – was very clear that "medicine is for the people, it is not for the profit; the profits will follow; the better we have remembered that the bigger they have been." So, it was this emphasis on science and that eventually good things would happen if you do good science.*

Drug research, in practice, is based on the findings of basic research (Drews 1999). Leaders of pharmaceutical firms working on radically innovative (drug) ideas need to be fully convinced that their novel knowledge and / or technology will lead to success. However, given that radical ideas tend to, by definition, be disagreed upon by others in the field, being convinced of future success can be a key challenge. Participant 3 mentioned that

> *radical breakthrough, by definition, means that not everybody agrees. I mean, if everybody would agree, then it would be obvious, and everybody would be working on this. So, if it's a radical breakthrough, then by definition, it must mean that there will be a few people saying, "That's a stupid idea. This will never work. We should not touch this. We should immediately*

stop this project." And so, you need somebody, a strong person in the project who will say, "I believe in this. I understand the science. I believe that this will work, let's go."

For leaders to be convinced about the potential success of novel scientific ideas, they must have a fundamental understanding of science. Participants 4, 7, 9, and 10 argued that top leaders of pharmaceutical firms dedicated to radical drug innovation should have sufficient scientific education and experience in pharmaceutical research. Participant 9 provided an example:

Well, the CEO of Merck during those glory years was Roy Vagelos. And Roy Vagelos was a physician-scientist, at his core. I mean, he came from the laboratory. He was a breakthrough scientist himself. He hired Ed Scolnick to be the head of Merck Research Labs, who was a phenomenal scientist. So, it came from the top. The CEO of the company was a physician-scientist and understood the value of breakthrough science. If you hired a commercial person as a CEO, they might rationally understand that science is important, but they haven't lived it themselves. So, one may think that commitment to science and innovation isn't quite as great. I'm sure there's some exceptions where non-scientists have been behind truly innovative companies because they saw the value. But starting with a physician-scientist is maybe a good start. Obviously, you need a good business sense, which Roy Vagelos also had.

This combination of deep scientific expertise and good business sense was also emphasized by Participant 4, who mentioned that

you need someone that can transform the idea into an asset, and the other guy needs to be the scientist that makes it happen somehow. Very often, those findings are kind of random findings. So, there needs to be this transformative step that someone understands at least enough of what's going on to transform this into a business idea or to transform this into an idea that gets it out of the lab and into an environment where it can grow.

Of course, these traits can be shared by one or more leaders of a pharmaceutical firm. If the top leader(s) of a pharmaceutical firm possess deep scientific expertise and believe in novel ideas, then they will be able to attract more external funding (Participant 10), and they will allocate appropriate resources to their (high-risk) projects (i.e., radically innovative drug candidates). As such, they can ignore (at least temporarily) the cost pressure often associated with the radical drug innovation process (Participant 7).

Moreover, such leaders are likely to **s**tay open-minded, be flexible, and follow the science, particularly "when the drug does not exactly do what you were planning it to do" (Participant 3). Top leaders need to expect the unexpected as a radically innovative drug candidate moves through the R&D phases. Effective leaders welcome unexpected results and do not see them as failures, as explained by Participant 5:

It's having that rightful skepticism in management that, going forward, helps them realize when they get a different result, it's not that unexpected. It doesn't mean you're wrong. It just means the hypothesis wasn't exactly as you thought. First in human is an experiment. The big thing that's actually improved a lot over the industry – it used to be you'd never measure anything other than what you needed to know, because you didn't want to find anything you had to explain out for the FDA. Unexpected findings are now viewed as a positive in many companies, because that's where a drug's really going to work. I've seen a lot of decreases of biomarkers, increases of endpoint imaging – a lot of that now…We realize we know so little about human biology it's crazy not to take information and gather it.

Participant 9 provided another example of top leaders' insistence on pushing forward during times of uncertainty:

But the top leadership of the company had the conviction that this pathway was going to work eventually. So, there was never any question that we would give up. There were a lot of lessons learned on how to develop drugs in this pathway. There was a belief that the failures were due to failed molecules, not a failed approach to the pathway, that these were individual drugs that were often liver-toxic or caused skin rashes because of the specific molecule itself, not the overall approach to the pathway. So, there was a lot of conviction from senior management to keep pushing ahead and learn from those mistakes or learn from those failures and eventually we would succeed.

A number of participants noted, however, that following the science must be done thoughtfully. As reported by Participant 7, it is a fine line between believing in science and believing in "your science":

I think many of those kind of innovative companies, they have the strong belief in their science and technology but many times…they eventually become very subjective. When you actually…that company, their believing in their science and technology – become so committed to that belief and become some kind of irrationally bias, that's actually quite dangerous.

Participants also noted that, in addition to having top leaders who possess deep scientific expertise and believe in novel ideas, it is critical – particularly in large pharmaceutical firms – to have a project champion who is committed to following the science. The importance of project champions for radical innovations is also discussed in the general innovation and entrepreneurship literature in particular (e.g., O'Connor et al. 2008; Selig et al. 2016). Participant 3 shared the following opinion:

We had a project that was on trace amines, and I think nothing ever came out. But this was driven by somebody who worked at the university on this particular class of targets, and he was also the project leader. And so, you always had a person there who knew everything about

this. And so, when there were project meetings and somebody would say, "In the recent issue of Science, there is a paper that says that if you block this receptor, you will get this toxic side effect," and [that person] would say, "Yes, I have read the paper. Don't worry, it's irrelevant for these reasons," and then everybody would relax, and he would go on.

4.5.2.2 Company culture of risk-taking, learning from mistakes, and accepting failure

The second most discussed firm-level determinant of radical drug innovation is a culture that fosters risk-taking, learning from mistakes, and accepting failure. This determinant is closely related to the previously discussed determinant (i.e., a company culture rooted in *following the science*). Firms that are led by science must go wherever the science takes them – a process that inevitably involves many risks, mistakes, and failures. Engaging in the development of radically innovative drugs (which are enabled by new scientific knowledge) requires leaders and scientists to expect the unexpected as their drug candidates move through the science-guided R&D phases.

Engaging in the development of radical drug innovation, which is associated with high risks, is a strategic choice because a pharmaceutical firm could instead focus on the less risky business of incremental drug innovation. Participant 9 gave an example to further explain this point:

If you're a big company…it may not make sense to take risks and fail multiple times. It might actually make sense to develop biosimilars, or, you know, the tenth TNF antagonist because the market is so big and even a small slice of that pie is selling $400 million or $500 million a year. And that's easy money. You know you're going to succeed, the pathways have been proven, and even if you're tenth to the market, you know, if you have contracting strategies that allow you to get onto formularies or you can negotiate better or your cost of goods is lower because of your scale, you know, you have other advantages that can make it financially successful, even for a tenth entry to the market. So, financially, it just is not completely clear that innovation is the way to go.

Leaders of pharmaceutical firms who make the intentional and conscious choice to engage in the development of radically innovative drugs need to shape and maintain a culture of risk-taking and learning from mistakes. This point was shared by all participants. As indicated by Participant 3, this type of culture makes explicitly clear that nobody will face consequences because of mistakes. Participant 4 further noted that

being safe in what you do is fundamentally important here in the U.S. So if you can tell them, and if you are credible in the way you create an environment where people feel safe about taking risks, and you have, if you want, a mechanism, or you have some role models that model

this behavior, I think that is very, very important, because people will not take risks if they have to fear tremendous consequences for their private lives, even.

Participants 1 and 2 communicated that a risk-taking culture and leaders who support and encourage this type of culture tend to make people feel accepting of mistakes, as well as willing to openly discuss them and to learn from them. People can only do this when they are convinced there will be no negative consequences in response to such mistakes. Participant 5 believes that regional cultural differences play a role here and that

it's one of the things they do well in the U.S., actually much better than England and Switzerland – accepting a culture of failure. Failure's not an issue. You get in a business where you know you're going to fail more times than you're going to succeed.

Participant 2 clarified, however, that all kinds of mistakes and failures should not necessarily be expected and tolerated. Although firms should expect and accept events such as a drug candidate showing high levels of toxicity in humans despite the absence of such signals in earlier (animal) studies, the types of failures that should not be expected or acceptable are human / operational mistakes such as incorrectly planning patient recruitment timelines for clinical trials. Mistakes such as these should be avoided at all costs.

Another core element of a risk-taking culture that should be communicated by leadership is to normalize failure and to make people feel comfortable with experiences that they define as failures. The intent is not to completely accept failure as the status quo, but to be comfortable with it and to see it as a sometimes necessary step in the process toward successful outcomes. As Participant 2 noted:

It's like comfort that, in order to really push the envelope, you're going to make some mistakes, but you need to learn from those mistakes quickly and keep growing… And part of it is normalizing mistakes. I'll see things like – even just this morning, as an example, we have an internal recognition system where you can say, "Thanks for doing this for me," that kind of thing.…I just saw this morning [on Slack] a scientist reaching out to an engineer and saying, in a way that was visible to the whole company, "I made a big mistake here. Thank you so much for helping me recover from this mistake"…it's like admitting to the whole company you've made a mistake, thanking the person that you reached out to, which was in a totally different function, for helping recover from this mistake, and just making it really visible. And I think it's really important to normalize that behavior, and the reaction can't be from that scientist's manager, "You made a mistake?!" It has to be, "Yeah, you made a mistake. We all have to help you solve it." And then when somebody helps, you thank them for it.

Strong, consistent, and thoughtful leadership is needed to build and sustain a culture that encourages risk-taking, learning from mistakes, and accepting failures, as there are

multiple barriers that need to be overcome on an ongoing basis. Of course, individuals naturally do not want to fail (as noted by Participants 9 and 10). Participant 10 reported that failing can be perceived as a career limitation, particularly in an "ecosystem where a lot of people have succeeded, and as I said earlier, even though they don't take failing against you, but not succeeding, versus somebody who actually succeeded." To address this important challenge, many venture capital (VC) firms, which often invest in pharmaceutical firms, use the approach described by Participant 10:

> *Most VCs, they have a position called entrepreneurial residence, and this is a position that allows people who go and take risks – if you take risks, and you fail, while you're looking for your next job, we actually hire you as a partner in our VC firm, and as a partner, we're going to put you on the board of a successful company, so that when it's time to go out, yes, you did fail your first endeavor. But you're also a board member of this company that has been very successful, so you mitigate the reputational risk that you have.*

In addition, as noted by Participants 1, 2, 3, 4, and 9, many scientists inherently dislike mistakes. Thus, according to Participant 2, it is critical to constantly remind these individuals that working on transformational ideas and radically innovative drug candidates comes along with high failure rates. Leadership needs to reinforce to their scientists and other employees that mistakes and failures are expected when attempting to deliver radically innovative outputs.

Lastly, Participants 3, 4, 5, 6, and 10 discussed firm-level barriers – in terms of management decisions and practices – to establishing a risk-taking culture. They reported that risk-aversion, which many firms operationalize through their R&D portfolio management approach, are associated with risk assessments of early-stage drug candidates that are too rigorous and, thus, hinder radical drug innovation. As noted by Participant 4:

> *It is very important to understand the risks, but it's also, I think, equally important to realize that many risks cannot be truly and quantitatively understood or described, and all the models that suggest differently are wrong because we don't know what we haven't done. And I think it's just, let's say, a false feeling of safety if you get a number of risk from 1 to 10, and the risk is 7, and you would decide, for whatever reason, since this is a 7, we will stop this. I think it's extremely important to be aware of risk and to constantly monitor and be aware of mitigation strategies and what not, but it's also – that's what I meant with being bold and having the courage of risk-taking. It's perfectly okay to take risks, as long as you know that you are taking risks and have certain strategies to potentially reduce the risk, being very, very informed in the way you're taking risks.*

According to Participant 4 and others, risk assessments of drug candidates in very early R&D stages should not be too rigorous because there are only very limited data available to assess

the risks and sales potential of such drugs. Many firms rate the risk level of their drug candidates on a specific scale (e.g., 1 to 10) and then all drug candidates that are perceived as too risky (e.g., above a threshold of 7) are stopped. The sentiment expressed by participants in the current study is that there should not be such a rigorous cutoff point for early-stage drug candidates given the limited data available about them.

Participant 6 stressed that having the right performance management metrics to foster radical drug innovation is essential for creating a culture that supports risk-taking and learning from mistakes. This is also stressed in the entrepreneurship literature; namely that goals for radical innovation projects should not be too specific (O'Connor et al. 2008). For example, when the performance of employees in R&D organizations is assessed by the number of drug candidates that successfully transition from one R&D stage to the next (which is still a common practice in many large pharmaceutical firms), risk-taking in the organization is often limited as a result. In such cases, employees tend to determine that it is preferable to focus on incrementally innovative drugs rather than radical ones, because incrementally innovative drugs are less risky and, as a result, more likely to progress along the R&D process and reflect more positively in the employees' performance assessments.

Of course, the right performance management metric depends on a firm's corporate objectives. If a firm is dedicated to radical drug innovation, they should assess the radicalness of the drugs that they bring to the market (i.e., the impact) – not just the quantity of the drugs. However, this can be somewhat challenging, given that the level of radicalness of a drug candidate tends to only show itself very late in the R&D process (which typically spans from 12 to 14 years). This may be at least one reason why many firms instead assess R&D performance based on the number of drug candidates that move from one R&D phase to the next. Participant 3 provided the following suggestion for a metric that encourages radical drug innovation:

> *Maybe it should be the other way around. Maybe there should be a policy saying, "These are our internal criteria for radical breakthrough innovations, and we need to have at least half of the molecules that go into Phase I, must have this breakthrough label." And if we have less, then it's not good, because, in the end, we have too many me-too projects in our pipeline. It's not good. So, instead of saying, "How many molecules will make it to the market per year?" it's saying, "We need to have a certain number of breakthroughs in Phase I."*

4.5.2.3 Leadership and decision making

The *leadership and decision-making* determinant is directly related to the first two firm-level determinants that were discussed above (i.e., a company culture rooted in *following the science* and *risk-taking, learning from mistakes, and accepting failure*). These determinants go hand in hand because the shaping and maintaining of firm culture is one of the primary objectives of firms' senior leaders.

The culture, and as such, the leadership needs, of pharmaceutical firms differ for early-stage (i.e., science-driven start-ups) versus large pharmaceutical firms with diverse business functions such as R&D, manufacturing, and marketing and sales. Top leaders of small firms should be science-driven (Participants 4, 7, 9, and 10). They need to have strong academic reputations and, ideally, be perceived as thought leaders in their field. They should be able to understand the radical science behind their drug candidates (Participants 9 and 10). In this sense, vast expertise is critical, as explained by Participant 10:

> *It's very hard to have a Zuckerberg in drug development – where somebody in college comes up with an idea about drugs, and suddenly that works. So, I think experience still matters.*

In addition to being science-driven, top leaders of pharmaceutical firms need to be business-savvy (Participants 4 and 9). Participant 4 believes that a transformative step is required to associate a radically innovative invention with a business opportunity. In other words, leaders need to be able to identify and recognize radical innovations as commercial opportunities. A useful example can be seen by looking at the efforts of the late venture capitalist Robert Swanson and the biochemist Dr. Herbert Boyer, whose capacity for forward thinking resulted in founding Genentech out of the radically innovative concept of recombinant DNA technology (Genentech n.d.).

Lastly, top leaders of small pharmaceutical firms dedicated to the R&D of radically innovative drugs are most effective when they are personally invested in their firms (i.e., when the leaders themselves engage in personal risk-taking to see that radically innovative drugs get developed). And personal risk-taking is not limited only to the financial realm, as reported by Participant 4:

> *I think this risk-taking and this, if you want, kind of ownership, where the boundaries of professional to personal investment – and I mean this not from a financial perspective. It could be, but it's not only a financial perspective. If that is more fluid, and if you have much more investment from people that work on a project than you would usually have in a highly regulated, professional environment, this is, I think, one of the key factors that enables you to*

have a higher likelihood of getting, I think, really disruptive techniques or methods or targets in the space of biotech in general.

Large pharmaceutical firms require different forms of culture, and thus, leadership from their top leaders. Leaders of large firms should be mainly focused on establishing a vision and strategy as well as ensuring optimal performance.

As a result of the differences in leadership requirements for small versus large pharmaceutical firms, CEOs of small firms frequently get replaced when their firms expand to greater complexity and size. Participant 10 described the approach of venture capital firms that invest in small pharmaceutical firms:

So, I would say in about 60% of the cases, we would replace the CEO, and this is almost systematic. The CEO who's going to take you to get your first milestone, scientific milestone, or the second, is not the one who's going to grow the company. And usually, this has been an understanding. The science guy comes first. They explore, trailblaze, and stuff. And then you realize that suddenly it's a 50-person company. Now you need people to be trained in actually running a company and understanding all stakeholders. And in general, the initial CEO moves into a CSO role or chairman, and then you bring somebody – you asked me what I saw about the science background versus the more general manager. When you reach the 50 to more, then the general manager has an incredible advantage, because they don't need to know the science in detail, but they need to know how to create a company and how to run the company and how to negotiate. The scientists are usually incredibly bad negotiators when it comes to selling the company.

All participants discussed shaping the firm's culture as a key leadership task that is important for the development of radical drug innovation, irrespective of firm size. As discussed above, a culture that is rooted in *following the science* as well as *risk-taking, learning from mistakes, and accepting failure* is essential for the development of radically innovative drugs. As such, it is critical for top leaders to create and maintain such a culture, irrespective of firm size. Participant 5 emphasized the need to embed a clear purpose in the firm culture and to ensure that employees stay focused on the core values and goals associated with their work, particularly in an environment of risk-taking and failure: "You keep people's eye on what the prize is. It's treating people – what we do with pharmaceuticals, for the most part, is incredibly important, right?" However, as noted by Participant 2, it can be challenging to scale this type of firm culture when a firm grows larger and more complex:

And so, after our Series C, we essentially had this hyper-growth period where we almost doubled the size of the company. And that's really hard. It's exhausting. It's exhausting to maintain a really, really high bar for hiring the people that you know not only have all the

scientific and the technical skills, but are also going to be good cultural adds to the company, are going to get excited about breaking barriers and doing things different.

Decision-making is a critical process and skill for effective leadership and business outcomes within firms. Many participants discussed the challenges of decision-making processes in large firms, recognizing that decision-making in small firms tends to be much faster and effective due to lower levels of complexities, including the number of stakeholders (Participant 1). Participants 1, 3, 5, 8, and 10 critiqued large firms' decision-making processes that occur through R&D governance committees (groups – versus a single decision-maker – that decide if a drug candidate will progress through the development stages or get terminated), primarily for the following two reasons. First, as explained by Participant 5, "committees never discovered anything new. Committees get the thing down to the narrowest mind in the room." So, if the decision-making process to advance (or not) drug candidates through the R&D phases is based on a consensus-seeking governance committee decision, then this might reduce the probability of advancing radically innovative drug candidates due to limited scientific expertise and / or risk aversion of some committee members. Both Participants 3 and 5 argued in favor of more distributed (i.e., decentralized) R&D decision-making processes: "What you really want is a bunch of independent people all making very different bets…Most of them will be wrong, but that one which has just come through will be successful" (Participant 5). Along this line of argumentation, Participant 3 questioned why a pharmaceutical firm would hire the best scientists and then tell them what to do:

You know, you have an idea, then you have to go to a committee, and the committee will say, "Okay, but first go back to your lab and make experiments to answer these three questions." And then you do this, and you go again to the committee and the committee says, "Okay, we'll enter this into our portfolio." And then you have to do this regular review, and then your projects run into trouble because you cannot repeat something. And then, some portfolio committee meeting member will say, "Well, sorry. There's not enough progress. We have to stop this project"...So that is the key decision. If you have a process where you can bring really very good scientists in the organization, then you can trust them, and you don't need to control them so much. Maybe you need to tell them a little bit how drug discovery works and what actually are the type of data that they need to present, so that the organization gets excited about a project. But otherwise, they can do whatever they like. So, it's spend and invest more in bringing really good scientists into the organization.

The second critique of large firms' decision-making processes through R&D governance committees is their slowness, particularly for very large pharmaceutical firms with

many stakeholders and heavy reliance on many governance committees. Participant 8 suggested minimizing governance decisions to the lowest possible level: "But it is a constant struggle, because it is the team versus the therapy area versus functions. You need to be very careful that there is not an overburden about keeping everyone informed through a cohort of governance meetings."

Given the need to effectively manage large portfolios of drug candidates and to increase the probability of successfully developing radically innovative drugs in large firms, both Participants 5 and 8 believe that a single decision-maker is critical. Participant 8 provided the following example:

> *It works really well, because you know, everyone openly puts their feedback in. I'm not just voting because of the safety [i.e., the functional R&D organization to ensure that a drug candidate is safe to be used in humans]. I have to look at the entire program and how do I see it?…and everyone has read it...and the presentation focuses on the comments. It's not the presentation from A to Z. It's kind of, we've got the teams coming and saying we've got the following comments. We're going to just now respond to the comments, and then my boss makes the ultimate decision.*

In other words, well-functioning R&D governance committees have a single decision-maker who chairs the committee and gets input from the various R&D functional experts on their committees. For the development of radical drug innovations, this format of having a single individual who is ultimately responsible for decision-making is preferred over consensus-seeking governance committees.

4.5.2.4 Firm size

There is a common belief among all participants that small firms are essential for radical drug innovations. Participants 1, 3, 4, and 10 reported that many (if not most) disruptive ideas and technologies, which might eventually turn into radically innovative drugs, typically originate in academic institutions and then get converted into assets in the form of small pharmaceutical start-up firms (e.g., through spin-offs from universities; Participant 4).

> *For truly disruptive things, it's not that you build a company and think about, "Oh, what could I do so that it is truly disruptive?" The idea comes first, and then you say, "Oh, gosh, this is actually something where we could potentially form a business." And I would argue, again, in the different categories where disruptive innovation could take place, at the very early stage, a lot of new druggable targets do come out of academic research. And very often, spin-offs from academia are the first to work on a truly disruptive therapeutic approach. And that is probably*

> *more than 80% of all the cases that I know–this is the way it goes. It comes out of a truly research-driven, non-commercial environment where you had freedom to research, and "freedom" is in parentheses, because there is no such thing as ultimate freedom, but you had a very poorly-regulated environment, and you would do whatever you wanted to do. (Participant 4)*

As such, these types of small firms are frequently 'born' from a disruptive idea – when people take personal risks in the form of founding, owning, and running a pharmaceutical start-up firm "where the boundaries of professional to personal investment...[are] more fluid, and…you have much more investment from people that work on a project than you would usually have in a highly regulated, professional environment" (Participant 4).

Small pharmaceutical firms, when compared to large ones, offer many advantages for the development of radically innovative ideas and technologies. For example, according to Participants 1 and 10, it is easier to establish and sustain a science-driven culture (a criterion of success with regard to radically innovative drugs) in small firms than it is in large firms. This may be because disruptive ideas and technologies tend to be at least somewhat controversial and vulnerable to disagreements among a firms' employees. As a result, it is often much easier to align everyone behind a disruptive idea or technology in a small firm than it is in a large firm, where there are more people to convince (Participant 9). Moreover, small firms tend to have a very clear organizational and operational focus because they typically have only one asset (i.e., drug candidate) to develop and, thus, no opportunity costs (Participant 5). As a consequence, everyone is strongly determined to win because otherwise, the firm will fail. As explained by Participant 3:

> *Everybody knows that if they are successful, then everybody is successful, and if this does not work, then the company will disappear and everybody will lose their jobs. So, the focus is very clear.*

Participants also discussed some disadvantages of small firms when it comes to developing radically innovative drugs. Participants 3, 6, and 10 noted that a key limitation of small firms is their inability to develop drugs through the clinical testing stages, which require high levels of technical expertise, resources, and global reach (for clinical trials). Participant 6 further explained this critical point:

> *When you have a new molecule, a small biotech company, it's not an innovative drug, it's just a molecule which might have the potential to become an innovative drug. I think the innovative drug, in the end, becomes clear maybe in Phase II when you can see the clinical outcome of a molecule, and then you can start speaking about a real innovation in the area or in this field.*

Before that, it's just a molecule and you think that this molecule could act better than what is already on the market. And of course, small biotech companies cannot. They need alliances because they cannot scope for the complete development costs, and also for the knowledge; they do not have this.

While small firms have the expertise and focus to do the initial research (i.e., front-end innovation) needed for radical drug innovation, they typically lack the expertise, resources, and global reach to develop such drug candidates through the later stages of the R&D process (Participant 10). And from an overall business point of view, it is not advantageous to build such (expensive) capabilities for the development of the one or two drug candidates typically carried out by small pharmaceutical firms.

This disadvantage of small firms points to one key advantage of large pharmaceutical firms: They have the technical expertise, financial strength, and global infrastructure to develop drug candidates through closely regulated clinical trials (Participants 3, 6, and 10). It is also easier for large firms to attract and retain relevant technical experts, as large firms are perceived as less risky and more stable than small firms because they do not depend on the success of just one or two drug candidates.

However, advantages of large pharmaceutical firms often get overshadowed by their frequent tendency toward risk-averseness. For example, Participants 1 and 4 explained that radically innovative drugs pose inherent reputational risks for large firms because such drugs might show safety problems in patients over time, which might lead to regulatory restrictions or withdrawals of the drugs:

If you're going with too much risk into a kind of a novel mechanism of action, you might be blamed or accused or whatever for that you haven't looked into everything for the patient's safety. And that might risk your other portfolio. So, if you're – whatever – if you're making billions and billions of sales and all of a sudden your reputation is ruined, then you might affect also all of the other drugs as well. That is why it is sometimes a little bit more difficult for larger companies to really test new ways of working. (Participant 1)

Relationships between large pharmaceutical firms and regulatory authorities such as the FDA and the EMA are established through many years of interactions (when developing drug candidates). Thus, large pharmaceutical firms might not want to risk their reputations with regulatory authorities by developing and commercializing radically innovative drugs (Participant 4).

An additional disadvantage of large pharmaceutical firms (with regard to the development of radically innovative drugs) that was reported by participants involves a lack of

focus, which is in contrast to the clear focus of small firms discussed above. Participant 10 explained that large pharmaceutical firms typically work on many different drug candidates in various disease areas because doing so is interesting, promising, and technically possible. However, when such large portfolios of drug candidates are not adequately managed in terms of which drugs should progress and which should not, many resources and much attention will be given to drug candidates that are ultimately unsuccessful. This point was further explained by Participant 6:

> *I asked just one question: "What do you think you can do with these projects in the next 2 years that you will come up better?" Because they were all asking for more time and money again so that they can live for another 1 or 2 years. And I only asked this question: "What do you think you will know in 2 years that you haven't known in the last 8 years with knowledge you have generated?" And there was a big quietness. And I said that, in the end, we have shut down, we have terminated this project. Because we really need this expectation that you have to set up milestones – I mean, feasible milestones. You cannot say, "Look, I want this drug in 1 year." But, feasible milestones. And if a project cannot deliver, then you really have to think about is it really worth it to go down this route, or is it already we are over the top and it will not work out how we have thought a drug might work?*

The lack of focus associated with large pharmaceutical firms can partly be explained by the fact that many employees in these firms do not depend on a drug's success for their personal career development and stability. Participant 10 (who works at a venture firm now, but previously worked at one of the largest pharmaceutical firms in the world) provided the following example:

> *My pay right now is dependent on how successful we are. But at [a large pharmaceutical firm], I get my RSUs. I get my stock options. As long as I don't get fired, I just wait, and after 3 years, just vest. Right now, it's not like that. If you're not successful, you're making less money. If you're successful, I can make really good money. So, everything is made in a way that's purely performance based.*

All participants in this study believe that small pharmaceutical firms are essential for the initial research of radically innovative drugs and that large pharmaceutical firms are important for the clinical development and scaling of drug candidates. Thus, there is a symbiosis between small and large pharmaceutical firms that is critical for the development of radically innovative drugs. Small firms carry out the initial research to develop disruptive ideas and / or technologies into molecules (which are not drug candidates yet). The expertise, resources, and global reach of large firms allows them to then convert these molecules into

drug candidates and develop the drug candidates through closely regulated clinical trials. Although this division of labor between small and large pharmaceutical firms is typical, it should be noted that there are a few large firms that independently develop their own radically innovative drugs, as explained by Participant 4:

> *Disruptive innovation can be done in big companies…and for many good reasons, there is also radically innovative research and development going on in big companies. What I would say is, it's a little bit like living in a big city. When we moved to Tokyo, I was horrified, because Tokyo is such a huge city, and I felt like wherever we would live, I would feel like swimming in the ocean and not knowing where my neighbor is and not knowing anyone. But the reality is that Tokyo is a beautiful city, and it's great living. And why is that? Because you are in a little neighborhood, and the neighborhood works like a little village within this mega-town, within this mega-city, so you don't feel like you live in this extremely large city, but actually you are at home in your little neighborhood. And there are maybe two or three thousand people in families, and that's where you make your friends, and that's where you are. And in big companies, it's also that way, so basically, you need to find your environment. You need to find your neighborhood, and then you can have a fantastic work / life environment, where you can flourish, where you can grow, and where kind of crazy ideas can also be pursued in a certain frame.*

It is also worthwhile to note that the symbiosis between small and large pharmaceutical firms might be challenging to observe empirically because of the high level of acquisitions in the pharmaceutical industry (Participants 3, 4, 7, and 10). Large pharmaceutical firms tend to acquire small ones to get full access to their disruptive molecules and / or technologies. In fact, the business model of most small pharmaceutical firms involves getting acquired by a large firm (Participants 4 and 10).

> *This is what flies for small companies, and for 80% of the ideas that I've spoken about, only 20% survive, and maybe 18% of those 20% overall will be acquired by pharma companies, and the residual 2% try to make their own way to develop a drug and eventually bring it to the market. (Participant 4)*

4.5.2.5 External knowledge sourcing

Most new knowledge that might eventually lead to the development of radically innovative drugs originates outside of an individual firm. According to some participants, as much as 80 to 99.9 per cent of new ideas and knowledge that result in radical innovations come from institutions that are external to individual pharmaceutical firms (Participants 3, 4, and 8). As such, R&D collaborations between research institutions, small pharmaceutical firms (start-

ups), and large pharmaceutical firms are very common. In fact, there is a well-established ecosystem, which Participant 7 referred to as a *tri-party model*, between academic research institutions, start-ups, and large pharmaceutical firms.

Participant 7 provided an example of a successful tri-party model: the development of the CAR-T technology platform. The first T-cell was engineered more than 30 years ago by Zelig Eshhar and Gideon Gross at the Weizmann Institute of Science in Israel (Styczyński 2020). The technology was then further developed (e.g., for novel oncology drug candidates) by start-up firms such as Juno Therapeutics (founded in 2013). Juno Therapeutics was acquired by Celgene for 9 billion U.S. dollars in 2018 (Lombardo 2018). Bristol-Myers Squibb then acquired Celgene for 74 billion U.S. dollars in 2019 (Hopkins and Al-Muslim 2019).

Participants in the current study discussed various strategies for accessing external knowledge that go beyond the common ways of external knowledge sourcing (e.g., co-development agreements, in-licensing agreements, and mergers & acquisitions). Participant 3 talked about post-doc fellowship programs, which provide a platform for post-docs to pursue independent research at pharmaceutical firms and to publish their knowledge and findings. Pharmaceutical firms that provide such fellowship programs build in-house expertise on state-of-the-art research. Participants 6 and 8 discussed scientific advisory boards as a source of external knowledge. Scientific advisory boards play an important role in directing R&D activities by bringing together leading experts in relevant diseases and therapeutic areas, as well as challenging and guiding internal R&D expertise / thinking. Participant 9 noted investigator-sponsored trials as a way to get access to external knowledge. In investigator-sponsored trials, drug candidates are given to academic investigators, along with modest stipends, who then study different diseases of their interest and share their results with the host company.

Lastly, for large pharmaceutical firms to engage in R&D collaborations with research institutes and small pharmaceutical firms, they must first build and maintain high levels of in-house scientific absorptive capacity (Participants 3 and 8). In this way, large pharmaceutical firms effectively identify themselves (e.g., through academic publications) as experts in certain research fields. This type of reputation, in turn, attracts small firms that are searching for development partners for drug candidates in these research fields.

> *But we'd rather know, based on the publications, they have a couple of really key experts. They probably have a fantastic network that would be great for us to tap into, because through that network, we can further grow. (Participant 8)*

Likewise, high levels of scientific absorptive capacity allow large pharmaceutical firms to identify and absorb external breakthrough knowledge. Pharmaceutical firms with high levels of in-house scientific expertise in specific areas are more likely to potentially identify and access external novel scientific ideas and inventions that are relevant for these areas. Firms without such deep in-house scientific expertise tend to not recognize or understand the significance of novel ideas, technologies, or findings.

4.5.2.6 R&D investments

There was clear agreement among all participants that for radical drug innovation to be successful, sufficient R&D funding is needed to pay for necessary basic science research, clinical trials, and development of new manufacturing processes for drug candidates that are based on new technologies (e.g., monoclonal antibodies, antibody-drug conjugates, or CAR-T). However, all participants also reported that focused investments are more important than absolute numbers of R&D spend. As reported by Participant 9: "You can throw money, but that doesn't guarantee anything. You just do stuff with money, but if you're not focusing it in the right way, it's money not well spent." Participant 8 further explained that when R&D funding is particularly high and / or unfocused, firms are likely to explore many different options (because they are all interesting), many of which will be stopped because "there is a risk if something doesn't look immediately as promising, you give up easily and move on to something else" (Participant 8). Participants 1 and 5 also noted that some of the largest pharmaceutical firms in the world (in terms of absolute R&D investment) are not perceived as the most innovative pharmaceutical firms. Participant 9 provided an example about how a pharmaceutical firm can develop radically innovative drugs with limited, but focused R&D investments:

> *One good example from the company Immunex that developed Enbrel, was they knew pretty early on that the drug would work in rheumatoid arthritis. And what they did – and they focused on rheumatoid arthritis, because they were a small biotech company, and they could only run so many clinical trials at the same time. But what they also understood is that there's a lot of potential disease states out there that might be responsive to a TNF antagonist, and they didn't have the human resources or the money to study them all. But they were able to create an investigator-sponsored studies program where they gave away the drug to interested academic investigators and a very modest stipend for them to study all these different diseases. So in a way, you had multiple shots on goal. They at one point had 80 investigator-sponsored studies ongoing from academics in multiple, multiple diseases. And out of that came two enormous*

successes. So one of them was ankylosing spondylitis, where an academic studied it. And another one was psoriatic arthritis. And everyone was shocked when those two studies came back shockingly positive. And then the company internalized the program and did the proper clinical trials to get an indication.

Other participants argued that, in addition to having sufficient and focused R&D investments, milestone-driven R&D spending is a critical success criterion for the development of radical drug innovation. Participant 10 noted that too much upfront R&D funding might lead to unfocused exploration and unnecessary organizational complexities:

There's a very delicate balance between giving them plenty of resources and saying, "Don't think about anything. Just go and work it out." What happens, we've found, in general, is that when you do that, you essentially reproduce what goes on inside of big pharma. People are no longer hungry. People are no longer – they don't see the urgency, and they don't do the bootstraps that we expect them to do. So, for example, as an organization that funds companies, we are locked now into tranching our funding. Yes, we're going to promise you that we're going to give you 60 million, but you're getting 10 now, and we have to see a result before we give the next 10, and then we have to see milestone-driven financing. And the reason why we did that is that it's like when I tried to lose weight. You can do whatever you want, but if you're tracking your calorie intake, every day you're getting on the scale where you feel like, "Oh, I'm not making progress," or "I'm making progress" – that's where you lose weight. And we feel like this is the same way that drug development is. You have to have smart people. They have to tackle difficult-to-solve problems. And they have to be resource constrained to some extent, so that they look for ways, ways to solve problems, and their brain just keeps thinking, "How am I going to solve this, given that I have this constraint?" You throw them a lot of resources, a lot, and you see that they're thinking differently, and they're constantly thinking about adding more resources, like people, hiring more people to solve their problems, instead of them finding ways to do it.

This milestone-driven investment approach explained by Participant 10 is common among venture capital firms that invest in small pharmaceutical firms. Large pharmaceutical firms with large portfolios of drug candidates often try to operationalize this milestone-driven investment concept through their portfolio management (i.e., stage-gate) process. The basic idea is that drug candidates need to meet pre-established criteria (e.g., in terms of safety and biological target activity) before they can progress to the next R&D process stage (e.g., entry into human). However, as explained by Participant 8, this requires a rigorous process:

You know, I'd say we had, until 2012, a much bigger R&D budget and percentage to our revenues than we have today. However, today we are much more successful than we had been

in the past. It has to do with, I would say, rigorous decision making. Rather than, "Okay, let's go for another round. Okay, we have the money, so let's try another trial. Let's do another Phase II study." Being more rigorous about your spend, and then having higher expectations that something really key is delivered according to the agreed contract, with the go / no-go's.

Lastly, Participant 3 highlighted an important limitation associated with shifting additional, firm-level R&D investments from one disease area to another. On a firm-level, R&D investments are typically a zero-sum game – if a firm decides to invest more R&D resources in oncology, for example, funding for some other area of research (e.g., cardiovascular diseases) needs to be decreased. This issue is particularly important when it comes to attracting and retaining top scientists from academia who often desire certainty that a pharmaceutical firm is committed to conducting long-term research in a specific area. Leading scientists from academia, who are highly valuable for pharmaceutical firms interested in the development of radically innovative drugs, tend to only leave academia and join a pharmaceutical organization if they believe that the organization will continue to do research in her / his area of expertise. As such, pharmaceutical firms that enter new (more promising) therapeutic areas and discontinue their research efforts in other therapeutic areas (so that they can maintain their overall R&D investment in balance) are less likely to be able to attract and retain leading academics. Indeed, this seems to be a key reason why many top scientists in academia do not want to work for pharmaceutical firms.

In conclusion, sufficient R&D investments are critical, as long as they are focused, milestone-driven, and committed to certain disease areas.

4.6 Discussion

According to most participants (9 out of the 10), a radically innovative drug is defined through its novelty and therapeutic benefit (i.e., impact). As such, there was no doubt among the participants regarding the definition of radical drug innovation. This finding is in contrast to the definitional ambiguity discussed in the *Background* section. However, as the discussed case of the drug Solvaldi® to treat hepatitis C makes clear, drug novelty is not always a necessary condition to define a radically innovative drug, although additional therapeutic benefit is always a criterion. The novelty of a radically innovative drug was defined by most participants through the concept of being first-in-class and offering a new and unique mechanism of action for treating a medical condition. The therapeutic benefit of a drug was mainly defined by the participants through its impact on patients, in the form of clinically important improvements versus existing drugs (i.e., the current standard of care).

While the novelty of a drug might be determined and measured fairly easily (is it a first-in-class drug and / or based on a new technology?), the therapeutic impact is much more challenging to measure because this characteristic only becomes apparent during Phase II or Phase III clinical testing (i.e., 5 to 7 years after identifying the drug candidate). This challenge has a fundamental impact on the management of radical drug innovations within pharmaceutical firms because for most of the time that a drug candidate progresses through the R&D stages, it is not clear whether the drug candidate will indeed turn out to be a radically innovative drug. As such, most of the decisions whether to advance a drug candidate to the next stage of the R&D process are based on incomplete information.

As discussed in the *Background* section, to date, there is only limited empirical evidence available to guide researchers and practitioners regarding which firm-level determinants are likely to lead to successful radical drug innovation outputs (versus incremental ones). Moreover, the current literature, heretofore, has been mainly focused on examining *external knowledge sourcing*, *internal knowledge management*, *firm size*, and *R&D investments* as determinants of radical drug innovation. However, findings from the current study indicate that a *company culture* rooted in both *following the science* and *risk-taking, learning from mistakes, and accepting failure* are additional essential firm-level determinants of radical drug innovation. Notably, the research of Aagaard and Gertsen (2011), which is among the very limited number of papers that specifically examines the determinants of radical drug innovation through an exploratory case study of a global pharmaceutical firm, did not report any findings on the importance of a company culture rooted in following the science. Therefore, the current study's findings – the criticality of a company culture rooted in *following the science* and *risk-taking, learning from mistakes, and accepting failure* – adds an important insight to the literature.

Most of the decisions about whether to advance a drug candidate to the next stage of the R&D process are based on incomplete information. Thus, understanding, believing in, and *following the science* is of utmost criticality for the development of radically innovative drugs. This type of company culture is formed and maintained by the senior leaders of a firm, who need to have a deep scientific expertise of the novel scientific ideas and technologies that the firm is working on. With such expertise, leaders are more likely to stay open-minded, be flexible, and follow the science, particularly when a drug candidate moves through the R&D phases with unexpected results. Moreover, we argue that the fundamental importance of a company culture rooted in following the science needs to be further differentiated. Such a

culture is particularly important for pharmaceutical firms' departments and personnel that coordinate and implement FEI processes, which is typically the research organization (as opposed to the development organization) in large pharmaceutical firms. Consequently, the culture of large pharmaceutical firms needs to be more nuanced across the pharmaceutical value chain (i.e., ambidexterity – the ability to exploit and explore) to enable the development of radical drug innovations.

Moreover, a culture of *risk-taking, learning from mistakes, and accepting failure*, which is clearly linked to the cultural element of following the science, makes people feel comfortable with accepting mistakes and willing to openly discuss them and to learn from them. A prerequisite for this to happen is that scientists need to be convinced that there will be no negative consequences in response to such mistakes. The importance of such a culture has been initially described by Aagaard and Gertsen (2011) in the following way: "Radical pharmaceutical FEI can be supported through the facilitation of explorative teams with time dedicated for exploration of ideas and a common acceptance of failure in making FEI" (p. 339). Findings from the current study go even further. First, the participants of this study clarified the nature of failures that should be accepted – namely, that firms should expect and accept failures such as a drug candidate showing high levels of toxicity in humans despite the absence of such signals in earlier (animal) studies, hence leading to stopping the development of that candidate. However, the types of failures that should not be expected or acceptable are human / operational mistakes such as incorrectly planning patient recruitment timelines for clinical trials. Second, the participants of this study offered their insights about a potentially important barrier to a culture of risk-taking in large firms – large firms' tendency toward risk-aversion and fearing reputational damages with regulatory authorities. As such, large pharmaceutical firms interested in the development of radically innovative drugs should address this potential barrier through tailor-made strategies such as subsidiaries dedicated to the development of radically innovative drugs (which could shield the parent company from possible reputational risks).

Leadership and decision-making are additional determinants that are crucial for radical drug innovation and also clearly linked to the first two determinants just discussed. One of the primary accountabilities of firms' senior leaders is to shape and maintain the culture of their firms. Not much is currently known about the relationship between leadership and decision-making on the one hand and radical innovations within pharmaceutical firms on the other (Stiller et al. 2021). The findings from the current study suggest that the leadership needs (in

terms of what kind of culture needs to be shaped and maintained) of early-stage, science-driven start-ups are different from the needs of large pharmaceutical firms that comprise diverse business functions such as R&D, manufacturing, and marketing and sales. For small firms (which mainly focus on the initial research and early development of drug candidates), top leaders need to have a strong academic reputation as well as be science-driven, business-savvy, and personally invested in the company to shape and maintain a culture rooted in *following the science* and *risk-taking, learning from mistakes, and accepting failure*. In contrast, large pharmaceutical firms require different and more nuanced leadership from their top leaders. While top leaders of such firms need to focus on establishing a culture rooted in *following the science* and *risk-taking, learning from mistakes, and accepting failure* for their research organizations, such a culture is not necessary for the development organization or for other functional groups such as manufacturing and marketing and sales. Instead, these areas require a vision and strategy focused on ensuring performance. These findings are line with the research of both Supriyadi (2013) and Tzabbar and Margolis (2017), who show that scientific leadership is pivotal in early-stage research outcomes, but is less important during later drug development stages (where the goal is to turn a new drug candidate into a marketable drug), which is highly regulated and, as such, leaves less room for leaders to influence outcomes.

Findings from this study support the current understanding of the importance of *external knowledge sourcing*. For pharmaceutical firms to engage in R&D collaborations with research institutes and smaller pharmaceutical firms, they need to build and maintain high levels of in-house scientific absorptive capacity. In this way, large pharmaceutical firms identify themselves (e.g., through academic publications) as experts in certain research fields, which attracts smaller firms that are searching for development partners for drug candidates in these research fields. Likewise, high levels of scientific absorptive capacity allow large pharmaceutical firms to identify and absorb external breakthrough knowledge.

Current research indicates that higher levels of *R&D investments* in pharmaceutical firms lead to higher outputs of radical drug innovations (e.g., Arnold and Troyer 2016; Dunlap et al. 2014; Quintana-García and Benavides-Velasco 2011). However, findings from the current study offer a more nuanced perspective than we have seen to date. While R&D investments are generally important for the funding of R&D activities, it is critical for the development of radically innovative drugs that such investments are focused and milestone driven. Unconstrained R&D funding might lead to unfocused exploration and unnecessary organizational complexities.

There have been conflicting empirical results about whether large or small firms are more successful with regard to radical drug innovation. Indeed, the literature is currently not clear whether *firm size* has a direct impact on radical drug innovation at all because large firms tend to have more resources to invest in R&D (which would indicate an indirect connection between firm size and radical drug innovation output). Findings from the current study support the idea that small firms tend to be more innovative; there was a common belief among all participants that small firms are essential for radical drug innovations, which is in line with the extensive literature on entrepreneurship. Many disruptive ideas and technologies that might eventually turn into radically innovative drugs typically originate in academic institutions and then get converted into assets in the form of small pharmaceutical start-up firms (e.g., through spin-offs from universities). This does not mean that large pharmaceutical firms cannot develop radical drug innovations, but they need to overcome important hurdles such as risk-aversion and unfocused R&D investments (as discussed above) to do so.

Many of the aforementioned firm-level determinants of radical drug innovations are equally relevant for the development of radical innovations in general (i.e., in other industries). For example, O'Connor et al. (2008) emphasize the importance, regardless of the industry, of (1) individual leaders (personal attributes and organizational roles), (2) organizational processes and systems, and (3) a company culture focused on innovation as critical determinants of radical innovations. However, our research provides more nuanced and industry-specific insights and findings due to the setting in the pharmaceutical industry, which possesses rather unique characteristics (i.e., very lengthy, risky, and costly R&D, which is mainly science-driven instead of based on customers' needs).

While the general innovation literature (e.g., Crossan and Apaydin 2010; O'Connor et al. 2008) and the literature on entrepreneurship in particular (e.g., Arshi and Burns 2018; Knošková 2015; Zhao 2005) point to a generally positive relationship between company culture (described in the literature in broad themes such as team work, valuing people, and time for learning and experimentation; Arshi and Burns 2018) and radical innovation, the results of the current study are more nuanced. Because the pharmaceutical R&D process is science-driven and most of the decisions about whether to advance a drug candidate to the next stage of the R&D process are based on incomplete information, understanding, believing in, and *following the science* is of utmost criticality for the development of radically innovative drugs. This particularity has implications for the specific attributes of senior leaders in pharmaceutical firms – they need to have a strong academic reputation as well as be science-driven to establish

and maintain a company culture rooted in following the science – something that is not that relevant in other industries.

4.7 Conclusions

Radical drug innovations are of great importance to pharmaceutical firms and to public health. Understanding the determinants involved in successful radical drug innovations is key to increasing this type of output in the future. Research to date has not provided a solid understanding of why some firms succeed in developing radical drug innovations while others do not, nor has it offered any conclusive evidence about which factors are critical for the successful development of radical drug innovations (versus incremental ones). It is known that all drug candidates go through similar R&D processes within a firm, regardless of whether the candidate might turn out to be radical or incremental. It is also known that the R&D process is set up and implemented relatively similarly across most pharmaceutical firms. It follows, then, that the organization and execution – at a macro level – of a pharmaceutical firm's R&D process does not seem to be a distinguishing criterion for radical innovation output. So, a more nuanced understanding of the firm-level determinants of radical drug innovation is needed. The current research took up this challenge. Semi-structured interviews with ten pharmaceutical experts were conducted to find answers to the overall research question of this study: *How do key firm-level determinants influence the development of radically innovative drugs; particularly with regard to the front-end innovation process?*

While most literature on this topic focuses de facto on four determinants of radical drug innovation (*access to external knowledge*, *internal knowledge management*, *firm size*, and *R&D investments*), the findings from the current study emphasize that the *culture* of a pharmaceutical company, particularly one that is rooted in *following the science* and in *risk-taking, learning from mistakes*, and *accepting failure*, is paramount for the development of radical drug innovations. Also, this study shows the criticality of *focused and constrained funding of R&D* as an important determinant of radical drug innovation development. Participants in this study made it clear that all of these firm-level determinants need to be managed equally. In other words, all of these firm-level determinants are critical for the successful development of radical drug innovations. However, more research from the inside of pharmaceutical firms is needed to further examine the relationships between key determinants and radical drug innovation. Thus, rich case studies as well as longitudinal and /

or experimental research are encouraged, particularly to examine the causal relationship between these determinants and radical drug innovation.

The findings from the current study also add to the literature on defining radical drug innovations. Despite the definitional ambiguity found in the current literature, radical drug innovation was unambiguously defined by the participants of this study through novelty *and* therapeutic benefit (i.e., impact) when compared to already existing drugs. Moreover, the findings from this study further strengthen the argument that drug novelty is not always a necessary condition to define a radically innovative drug, while additional therapeutic benefit is always a criterion. Although the novelty of a drug might be determined and measured fairly easily (is it a first-in-class drug and / or based on a new technology?), the therapeutic impact is much more challenging to measure because this characteristic only becomes apparent many years after identifying the drug candidate. Because of this, decision-makers within pharmaceutical firms often rely on incomplete information to make decisions about whether to advance a drug candidate to the next stage of the R&D process. This is a key barrier to the development of radical drug innovations and can be mitigated through a firm culture that is rooted in *following the science* and *risk-taking, learning from mistakes, and accepting failure.*

As with any study, the current research contains some limitations, which are partially the result of the chosen research method. First, a potential limitation of the study is its rather small number of interviews, which might limit the study's internal and external validity. Second, purposive and convenience sampling is an inherently biased method and might not allow for generalization of the research findings beyond the interviewed population. Third, there was a gender imbalance among the participants, which might have led to biased results. Fourth, the interview questions were shared with all participants prior to the interviews, which might have influenced their responses because they had time to think about their answers. Fifth, there might have been interviewer bias (e.g., through the attitude of the interviewer during the interviews), which might have impacted the interview outcomes. Sixth, the template analysis coding process might have reduced the data in such a way that led to a loss of interviewees' intended meanings. However, to address this potential limitation, the coding was carried out independently by two researchers.

The empirical evidence provided in this study will hopefully stimulate further research on the important topic of radical drug innovation and how to increase the output of radical drug innovations across pharmaceutical firms. More radical drug innovations are needed to deal with current unmet medical needs, especially given that approximately two-thirds of known diseases

cannot be effectively treated at this time (Claret 2016). Thus, additional research is needed to understand how pharmaceutical firms can most successfully respond to this need.

Chapter 5 | Conclusions

5.1 The research in an overall context

Innovation in a business environment, which is the focus of the current research, is, at its essence, an invention or new idea that is successfully commercialized (Kanter 1983). In this context, innovation can be understood either as an outcome (i.e., a new product or service) or as a process that leads to innovation as an outcome (Crossan and Apaydin 2010).

When innovations are understood as an outcome, one common way to distinguish the degree of the newness of the innovation is the dichotomous conceptualization as either incremental or radical. Innovations that are thought to be incremental, on the one hand, generally refer to minor changes to an existing product, service, or process that result in small impacts (Tushman and Anderson 1986). Radical innovations, on the other hand, typically represent a product, service, or process that is fundamentally new and significantly impactful. Radical innovations are critically important to many industries (Keupp and Gassmann 2013), and firms that deliver radical innovations frequently experience competitive advantages in the marketplace.

It is well established in the current literature that different organizational capabilities are needed for the development of radical versus incremental innovations. The resource-based view (RBV) of the firm argues that unique resource allocations at a firm level lead to the creation of innovations (Fagerberg et al. 2005). The knowledge-based view (KBV) of the firm, which is an extension of the RBV, adds that knowledge – and hence organizational learning – is a firm's most important resource for the creation of innovations (Curado 2006). Accordingly, firms need to manage their *resource allocations* and *organizational learning* differently to create radical instead of incremental innovations. Also, the process that leads to radical innovations needs to be managed differently than the process that leads to incremental innovations.

Many critical, firm-level innovation capabilities and processes are industry-specific. Consequently, the organizational capabilities needed for the development of radical (and incremental) innovations may vary across industries. As such, they need to be examined in an industry context and not generically. This especially applies to innovations in the pharmaceutical industry – i.e., drug innovations – because drug innovations are rather unique. For example, drug innovation is mainly science-driven and not, like innovations in most other industries, customer-driven. In addition, drug innovation is a very costly, risky, and lengthy process.

While the importance of radical drug innovations for public health and pharmaceutical firms is well established, researchers and practitioners have yet to agree on a single definition or to develop a validated measure for the concept of radical drug innovation. Innovation scholars continue to utilize untested measurement approaches to conduct research on the determinants and consequences of radical drug innovation. The lack of an agreed upon definition of, and measurement approach for, radical drug innovation limits our understanding of the concept, as well as its determinants and its impacts in real-world situations. Results from studies that intend to explore radical drug innovation theories, but that rely on untested measures of radical drug innovation, are difficult to make sense of and are potentially misleading or inaccurate. In addition, the utilization of different measurement approaches inhibits the comparison and integration of results across studies, thus limiting our ability to gain a comprehensive understanding of how radical drug innovations are successfully developed.

The research presented in this paper addresses the gaps noted above. First, a definition of radical drug innovation is offered. Second, the paper discusses and provides evidence of the limitations currently associated with radical drug innovation measurement and proposes a new, validated method based on the German health technology assessment (HTA) approach. This validated measure will enhance our ability to understand radical drug innovation and its firm-level determinants, to compare results across studies, and to stimulate additional research on the topic. Third, we present a systematic overview of what is currently known about the firm-level determinants that are important for the development of radical drug innovations. Fourth, through semi-structured interviews with pharmaceutical R&D experts, the current knowledge about firm-level determinants of radical drug innovation is further extended – particularly for determinants that are difficult to assess, such as leadership and a firm's culture. The following four research questions guided the current research:

1. *What constitutes radical drug innovations?*
2. *Do current measures of radical drug innovation actually assess what they purport to measure*
3. *What firm-level determinants are critical for the development of radically innovative drugs?*
4. *How do key firm-level determinants influence the development of radically innovative drugs; particularly with regard to the front-end innovation process?*

The findings for each of these research questions are discussed below.

5.2 Findings and discussion for each research question

Research question 1: What constitutes radical drug innovations?

There is little clarity in the current literature on what precisely constitutes radical drug innovation (de Solà-Morales et al. 2018; Morgan et al. 2008). As a consequence, it remains unclear "what kind of new products should be pursued, protected and encouraged through health policy and clinical practice" (Morgan et al. 2008, p. 4).

There are two findings from the current research that relate to the definition of radical drug innovation. First, the systematic literature review findings (Chapter 3) provide further empirical evidence for the definitional ambiguity of radical drug innovations in the current innovation literature: None of the 38 papers included in the systematic literature review provide a specific definition of radical drug innovation. Instead, roughly half of the papers (21/38) offer non-industry-specific definitions of the concept, despite the well-established claim in the literature that the definition of (radical) innovations are context-specific, and as such, industry-specific. The other half of the studies (17/38) do not provide any definition of radical drug innovation at all. This finding is in line with Kesselheim et al.'s (2013) systematic review, which excluded 84 per cent of articles because they did not contain definitions of drug innovation, and confirms a lack of scientific rigor in the current pharmaceutical innovation literature.

Second, despite the definitional ambiguity found in the current literature, radical drug innovation was unambiguously defined by pharmaceutical R&D experts who participated in our semi-structured interviews (Chapter 4). Thus, there seems to be a gap between the theoretical understanding of radical drug innovation in the current literature and the understanding of the concept among practitioners in the field. The pharmaceutical R&D experts who participated in this research defined drug innovation through the novelty *and* therapeutic benefit (i.e., impact) of a new drug when compared to already existing drugs. Most experts defined the *novelty* of a radically innovative drug through the concept of being first-in-class (i.e., drugs that offer a new, unique mechanism of action for treating a medical condition) or through the novelty of the underlying technology (e.g., the CAR-T technology to engineer patients' immune cells to treat their cancers; the CRISPR gene editing technology; or the Transport Vehicle (TV) technology to transport therapeutic proteins across the blood-brain barrier). These experts primarily defined the *therapeutic benefit* of a new drug through its

impact on patients when compared to improvements offered by existing drugs (i.e., the current standard of care).

With these findings in mind, we offer the following two-dimensional definition of radical drug innovation for future innovation research within the pharmaceutical industry: A new drug can be considered radically innovative if it (1) provides evidence for important additional therapeutic value (net of treatment risks) to patients when compared to already existing drugs that are intended to treat the same clinical condition and (2) is first-in-class.

Research question 2: Do current measures of radical drug innovation actually assess what they purport to measure?

As discussed throughout this research, innovations in general are difficult to study because of their abstract, intangible nature. The concept of radical drug innovation is no exception, and research on the topic suffers from a lack of definitional consensus and reliance on untested and varying measurement approaches. Researchers have used a wide variety of measures to assess radical drug innovations (mainly patent citations, NME classifications, and FDA Priority Reviews) without adequate testing and validation. Without testing and validation, we cannot know if these measures accurately assess the concept of radical drug innovation, which limits our ability to understand radical drug innovations as well as their determinants. One aim of the current research was to evaluate whether the most commonly used measures of radical drug innovation actually assess the concept. Findings from the current research – particularly the first study, which is presented in Chapter 2 – indicate that the most commonly used measures of radical drug innovation (which assess novelty via patent citations or NME classifications and therapeutic value through FDA Priority Review classifications) are associated with very inconsistent outcomes.

After discovering this result, we examined whether one of these measurement methods was preferable to the others. Based on our prior discussion about the definition of radical drug innovation (research question 1), particularly the point that a radically innovative drug is defined by its novelty *and* therapeutic value / impact, we argue that measures of drug innovation that are based solely on novelty (e.g., patent citations and NME classifications used on their own) are inherently flawed and should not be used to measure radical drug innovation. In addition, the current two-dimensional measure that assesses both novelty (through NME classifications) and therapeutic value (through FDA Priority Review designations) is potentially problematic. We argue that the two-dimensional measure is inadequate due to its

inclusion of the FDA Priority Review designation. One of the problems associated with this approach is that drugs approved through Priority Review may not actually result in the clinical outcomes that were anticipated during the review process. In addition, priority-reviewed drugs may be more likely than other drugs to have more risks than they have benefits. As such, we argue that the Priority Review classification should not be used to assess the therapeutic value of potentially radical drugs.

Given the issues associated with the most commonly used radical drug innovation measures, the current research proposes a new method based on the NME classification (as a measure of novelty) and Germany's HTA approach (as a measure of additional therapeutic drug value) instead of Priority Reviews. We selected the German HTA approach because it relies on clinical studies to measure the additional therapeutic value of new drugs versus the standard of care.

Using this new measurement method in the first study, we found that approximately 80 per cent of the 147 approved drugs examined do not offer important additional value versus existing alternatives. This finding supports our argument that relying on drug novelty alone does not allow us to effectively identify drugs that will deliver meaningful additional therapeutic value. As a result, we argue – in line with our discussion under research question 1 – that considering the comparative therapeutic value of drugs is necessary to understand their level of innovativeness. Moreover, we suggest that the assessment of therapeutic value is best achieved by the German HTA method because it always requires comparison of the new drug with an existing one (as opposed to Priority Reviews, which do not). Furthermore, when comparing the measurement results associated with the two assessment approaches (*NME + HTA* versus *NME + Priority Reviews*), we found notably different measurement outcomes. As such, HTA and Priority Reviews cannot be substituted for each other.

Also, the findings from this research further expand the current state of the art by offering evidence to support the argument that drug novelty is not always a necessary condition to define a radically innovative drug, while additional therapeutic benefit is always a criterion. Thus, the additional therapeutic benefit of a drug matters more than a drug's novelty. This argument is supported by the finding in Chapter 2 that the new measure of radical drug innovation is primarily determined by the additional therapeutic benefit of drug (i.e., the HTA indicator) because the effect of HTA on the construct is notably higher (beta = 0.906) than the effect of NME (beta = 0.207). This finding suggests that the novelty / NME component might not be a necessary element of the radical drug innovation measure, which would be an

important departure from the current understanding of radical drug innovations. However, one potential explanation for this finding provides a rationale for keeping novelty / NME included. According to Achilladelis and Antonakis (2001), pharmaceutical science and technology evolves by "quantum jumps, which are followed by periods of less adventurous steps along the established pathways" (p. 550). The lower significance of the NME indicator found in Chapter 2 may be explained by the fact that all 147 drugs entered the market between 2011 and 2016, and thus are all probably based on similar technology platforms. We believe that the impact of the NME classification on the construct will be likely more significant over time, and hence that the novelty / NME indicator should remain part of our recommended measure of radical drug innovation.

Research question 3: What firm-level determinants are critical for the development of radically innovative drugs?

Most pharmaceutical R&D activities and investments are risky endeavors because many decisions as to whether to advance a drug candidate to the next stage of the R&D process are based on incomplete information, as the therapeutic impact of a drug candidate only becomes apparent during Phase II or Phase III clinical testing (i.e., 5 to 7 years after identifying the drug candidate). This challenge has a fundamental impact on the management of radical drug innovations within pharmaceutical firms because for most of the time that a drug candidate progresses through the R&D stages, it is not clear whether it will eventually turn out to be radically innovative or not. As a consequence, it is critical for pharmaceutical firms to identify and understand relevant firm-level determinants for the successful development of radical drug innovations. Such understanding might help to decrease the risk associated with the pharmaceutical innovation process. In line with this, one of the objectives of the current research was to search the literature for key firm-level determinants of radical drug innovation. Following a systematic literature review approach, we considered more than 4,100 peer-reviewed journal articles and PhD theses, 38 of which were included in the final narrative synthesis.

The systematic literature review presented in Chapter 3 shows that there is still much work to do in developing our understanding of firm-level determinants within the pharmaceutical industry (i.e., radical drug innovation). Research in this field is still far from established, as is indicated by the low number of papers on this topic that we were able to identify. As such, our ability to understand and explain the determinants of radical drug

innovation is currently incomplete. The research that has been carried out on this topic has mainly focused on four firm-level determinants: *internal knowledge management, external knowledge sourcing, R&D investments,* and *firm size*.

New knowledge that may eventually lead to radical drug innovations (i.e., *internal knowledge*) can be created by investing in pharmaceutical R&D (i.e., *internal knowledge management*), particularly in the very early R&D stages (i.e., basic science research). A potential mechanism for this finding may be that the buildup of internal basic scientific knowledge generates more absorptive capacity, which enables company scientists to identify, absorb (e.g., through collaborations with top-tier research universities), and integrate critical external knowledge, thereby increasing the likelihood of developing radical drug innovations. Thus, there is a link to *external knowledge sourcing*.

Within the pharmaceutical industry, the front-end innovation (FEI) process (i.e., idea generation through disease biology understanding) relies heavily on external knowledge sourcing (because most new knowledge originates from outside of pharmaceutical firms). Findings from the current study suggest that the FEI process for pharmaceutical firms (as it relates to radical drug innovation) is still poorly understood. This is especially true for the later phases within the pharmaceutical FEI process (i.e., exploratory project discovery, drug discovery, and preclinical tests).

R&D investments and *firm size* represent two additional key determinants that tend to be discussed within the literature on radical drug innovation. However, based on the findings from the current research, we believe that these determinants are often presented and considered in ways that indicate an over-simplified understanding of the innovation process that leads to radical drug innovation and that treat the pharmaceutical innovation process like a black box. Our research indicates that more granular / micro-level aspects of these determinants are responsible for a firm's ability to deliver radical drug innovations. For example, we know from the literature that higher R&D spending is associated with greater outputs of radical drug innovations within the pharmaceutical industry. However, we do not know (from current empirical evidence) which phases of the innovation process are most beneficial to invest in. For leaders and managers who aim to increase radical drug innovation outputs, we need to develop guidance with regard to spending on the FEI / research phase versus the development phase (i.e., later stages of the R&D process). At this time, we only know that more money should be invested in pharmaceutical R&D overall, which is not very informative or helpful in a practical sense.

Previous research has also not provided enough clarity with regard to the impact of firm size on radical drug innovation. Our findings indicate that the relationship between firm size and radical drug innovation may be an indirect one. Given that large firms have more resources to invest in R&D, the increased levels of radical drug innovation outputs among large firms that some studies have shown may actually be the result of increased R&D (as opposed to firm size per se).

In addition, we were able to identify only a few studies that focus on *leadership* and / or a *firm's culture* as a key determinant of radical drug innovation. This is in contrast to evidence indicating that these two determinants are important for radical innovations in other industries. We believe that research on these determinants in pharmaceutical firms is likely limited because they are difficult to study within the environment of pharmaceutical firms, given the industry's need to protect intellectual property and knowledge. The few identified studies on the topic of leadership and radical drug innovation indicate that scientific leadership is more important for the early stage of innovation (i.e., the FEI phase) than it is for the later stage (i.e., the drug development phase). However, this differentiation is not found when we look at the relationship between radical drug innovation and a firm's culture. As is the case with R&D spending and firm size (as discussed above), the impact of a firm's culture on radical drug innovation tends to be examined more generically. Again, we argue for a more nuanced understanding of the relationship between this determinant (i.e., a firm's culture) and radical drug innovation.

Research question 4: How do key firm-level determinants influence the development of radically innovative drugs; particularly with regard to the front-end innovation process?

As evidenced by the results of the systematic literature review in Chapter 3 and discussed in the previous section, literature on key determinants for radical drug innovation primarily focuses on – in sometimes over-simplified ways – *external internal knowledge management*, *knowledge sourcing*, *firm size*, and *R&D investments*. A more nuanced understanding of the relationship between these determinants and radical drug innovation is needed. Also, much less is known about other firm-level determinants such as *leadership* and *company culture*, which have been found to be critical for radical innovations in other industries. Gassmann and Schweitzer (2014) argue that leadership, namely "being good at managing people, i.e., finding the right people, setting up a good network, coaching the teams, identifying the creative potential of the individuals and providing them with a strong vision and direction" (pp. 8-9) is

fundamental for the success of the FEI process. The FEI process is, in turn, critical for the development of radical innovation because it is during the FEI process when initial ideas (that may lead to radical innovations) are developed (Aagaard 2012, 2015; Nicholas 2014; Rice et al. 2001).

These challenges were taken on in the third study of the current research (presented in Chapter 4) through semi-structured interviews with pharmaceutical R&D experts from ten pharmaceutical firms and venture funds in the U.S., Switzerland, the UK, and Germany. Findings from this research indicate that a *company culture* rooted in both *following the science* as well as *risk-taking, learning from mistakes, and accepting failure* is an essential firm-level determinant of the FEI process and, as such, radical drug innovation. These results add important insights to our understanding of radical drug development.

Following the science – which requires also understanding and believing in the science – is of utmost criticality for the development of radically innovative drugs, especially given that most decisions about drug candidate advancement within the R&D process are made without complete information. As such, key decision makers must have a foundation to guide them – i.e., science. Pharmaceutical firms that are led by individuals with deep scientific expertise are more likely to be open-minded, be flexible, and follow the science, particularly when a drug candidate moves through the R&D phases with unexpected results. Consequently, *following the science* (as a key firm-level determinant of radical drug innovations) is a unique determinant for the pharmaceutical industry, as compared to other industries. This is due to the fact that the pharmaceutical innovation process is science-driven and not customer-need driven, as is the case in most other industries.

The likelihood of success in developing radically innovative drugs is also enhanced when pharmaceutical firms have a culture of *risk-taking, learning from mistakes, and accepting failure*. People working in such firms tend to feel more comfortable with accepting mistakes and are more willing to openly discuss them and learn from them. People are more likely to do the work that is needed for radical drug innovations when they feel sure that there will be no negative consequences in response to mistakes. However, large firms tend to be considerably risk-averse, and this tendency represents a potentially important barrier to a culture of risk-taking. As such, we recommend that large pharmaceutical firms interested in the development of radically innovative drugs attempt to break through this barrier. One strategy includes utilizing subsidiaries that are solely focused on the development of radically innovative drugs.

The current study shows that *leadership and decision-making* are additional important determinants for radical drug innovation and that senior leaders play a significant role in shaping and sustaining a firm's culture (which, as discussed above, is another key determinant of radical drug innovation). Our findings indicate that firms' leadership needs differ by the stage of the firm. More specifically, early-stage, science-driven start-ups that tend to focus on the initial research and early development of drug candidates have different needs compared to large pharmaceutical firms that carry out a variety of business functions such as R&D, manufacturing, and marketing and sales. Small, early-stage firms need leaders with a strong academic background who follow the science, as well as robust business opportunities. Ideally, these leaders are personally invested (not only financially) in the company and focus on shaping and sustaining an overall company culture rooted in *following the science* and *risk-taking, learning from mistakes, and accepting failure*. In contrast, leaders of large pharmaceutical firms are most effective when they differentiate cultures across different business departments. Although a culture rooted in *following the science* and *risk-taking, learning from mistakes, and accepting failure* is vitally important for research organizations within pharmaceutical firms, such a culture is not equally important for development organizations or for other functional groups such as manufacturing or marketing and sales (which would do better to focus on performance and standardization).

R&D spending represents another factor that plays a notable role in the success of developing radically innovative drugs. A good deal of research, as discussed under research question 3, indicates that higher levels of R&D spending are associated with greater radical drug innovation outputs (e.g., Arnold and Troyer 2016; Dunlap et al. 2014; Quintana-García and Benavides-Velasco 2011). Results from the current study provide a more nuanced perspective on this relationship. We find that firms are more likely to successfully develop radically innovative drugs when R&D investments are focused, constrained and milestone-driven and that firms with unconstrained R&D funding tend to not do as well. We recommend that leaders focus on clear, milestone-driven R&D spending in an effort to stave off the type of unfocused exploration and unnecessary organizational complexities that come with unconstrained R&D funding.

Previous research has shown conflicting results regarding the impact of *firm size* on radical drug innovation. As discussed above, it is not clear whether the positive relationship that some studies have found between firm size and radical drug innovation is a direct or indirect one, given that large firms tend to spend more on R&D than do small firms. Results

from the current research suggest, however, that the relationship is a direct one and that small firms tend to be more innovative than large firms. Indeed, most interview participants noted that small firms are necessary for radical drug innovations and that many disruptive ideas and technologies (which are often the foundation for radically innovative drugs) come from academic institutions and then get converted into assets in the form of small pharmaceutical start-up firms (e.g., through spin-offs from universities). Large firms do also create radically innovative drugs, but they must break through significant barriers such as risk-aversion and unfocused R&D investments (as discussed above) to do so.

5.3 Recommendations for future research

This research adds to the current literature on radical drug innovations in multiple ways and offers a platform on which to build future work. First, to further advance our understanding of the relevant firm-level determinants of radical drug innovation and to inspire additional research on the topic, this research (1) argues for the development and use of a validated measurement approach for radical drug innovations and (2) proposes a potential new measurement method based on the German HTA model. Additional research should be carried out to assess the utility of the HTA-based measurement approach for measuring radical drug innovations. We recommend that researchers utilize the HTA measure to explore key determinants and outcomes associated with radical drug innovations, comparing their results with those from studies that rely on different measurement tools.

Second, most research to date on the topic of radical drug innovation does not consider the process character of innovation or the interdependencies between the various process steps (and their influencing determinants). Instead, the current literature tends to describe the pharmaceutical innovation process as linear. As a result, studies typically examine firm-level determinants of radical drug innovation in isolation, neglecting the process character of, and relationships between, key factors. We suggest that future research examine how the structure and organization of innovation processes within pharmaceutical companies play a role in developing radical drug innovations. More specifically, we need research that explores differences and similarities in the process character between FEI / research phases (where more process flexibility is needed) and later clinical development phases (where less process flexibility is needed), as well as interactions between these phases. For example, it would be helpful to better understand how clinical trial results flow through feedback loops back to basic research, exploratory project discovery, and drug discovery organizations, thereby informing

ongoing and future work on radical drug candidates. This type of work is emphasized by the fourth-generation innovation models, which perceive the innovation process as running in parallel with feedback loops across various organizational functions.

Third, we recommend that future research examine how the evolution of the pharmaceutical innovation process from a closed networked innovation model (fifth-generation model) to an open innovation model (sixth generation) has impacted radical drug innovation. Schuhmacher et al. (2013) note that many pharmaceutical firms are "leaving the more traditional R&D model and […] reforming pharmaceutical R&D in the direction of open innovation" (p. 1136) to increase their R&D productivity by sourcing external drug candidates and decreasing in-house research activities (which tend to be quite costly). Although this type of transition likely decreases a firm's overall R&D costs, it also potentially reduces its absorptive capacity (Schuhmacher et al. 2013). This, in turn, may decrease the firm's ability to identify, source, and integrate the type of external knowledge that is so critical for radical drug innovation. Future research should examine the net benefits of open innovation on radical drug innovation, with a specific focus on the advantages of external partnerships versus the disadvantages of reduced absorptive capacity.

Lastly, more research from the inside of pharmaceutical firms is needed to further examine the relationships between key determinants and radical drug innovation. Thus, rich case studies as well as longitudinal and / or experimental intra-firm research studies are encouraged, particularly to explore the causal relationship between these determinants and radical drug innovation.

Chapter 6 | Appendix

6.1 Appendix – Interview guide

Introduction

- Purpose of this research: Radical / breakthrough drug innovations are difficult to create, yet they are of great importance to pharmaceutical firms and public health policy. Understanding the determinants involved in successful radical drug innovations is key to increasing this type of output in the future. To provide a more in-depth understanding of firm-level determinants in radical drug innovations, I'm conducting interviews with pharmaceutical experts like you today.
- Recording & confidentiality: This interview will take approximately 45 mins. If you agree, I'm going to record this interview so that I can transcribe it later on and analyze the interview data in an anonymous way. I won't disclose your name. If you prefer, I won't mention the name of your company either. We can stop the recording or the interview at any time without you giving me any reason.
- I'm trying to observe more than talk. As such, I won't interrupt you as much as possible.
- I'm going to refer to pharmaceutical firms as companies that are dedicated to the research, development and potentially the commercialization of pharmaceutical drugs. They include biotechnology firms.

Questions

[Note to interviewer: questions to help define the dependent variable (radical drug innovation)]:

1. In your opinion, what differentiates a radically innovative drug (or breakthrough drug) from all other drugs?
    a. Can you name an example of a drug that you believe is radically innovative / breakthrough drug?
    b. Can you name an example of a drug that you believe is not a radically innovative / breakthrough drug?
2. In your opinion, is there an objective way to identify / differentiate a radically innovative / breakthrough drug from non-radically innovative / non-breakthrough drugs?
    a. How?
    b. At which point in the product lifecycle?
3. In your opinion, do payers and pharmaceutical firms differentiate between a radically innovative / breakthrough drug and all other drugs (i.e., non-radically innovative / non-breakthrough drugs) in a similar way or are there differences?
4. Have you been personally involved in the development of a radically innovative / breakthrough drug?
    a. If so, when and how did you realize that you were working on a radically innovative / breakthrough drug?

[Note to interviewer: open questions to explore interviewee's insights about determinants of radical drug innovation]

5. Can you think of a context / scenario in which a firm can successfully develop a radically innovative / breakthrough drug? What is needed and what needs to be done so that it can happen?
6. What are possible challenges for a pharmaceutical firm to develop a radically innovative / breakthrough drug?
    a. What could be done to overcome these challenges?

[Note to interviewer: questions linked to Research Question 1: How do tangible firm-level determinants influence radical drug innovation output of a firm?]

7. In your opinion, are bigger or smaller firms more likely to develop a radically innovative / breakthrough drug? Why?
8. In your opinion, does the market dominance of a firm [e.g., think of large firms like Pfizer, Merck, Roche] give an advantage or disadvantage when developing a radically innovative / breakthrough drug? Why?
9. In your opinion, is there a relationship between how much a company invests in Research & Development and the firm's ability to develop a radically innovative / breakthrough drug?
    a. If not, what other factors do you think are important for a pharmaceutical firm to develop a radically innovative / breakthrough drug?

[Note to interviewer: questions linked to Research Question 2: How do intangible firm-level determinants influence radical drug innovation output of a firm?]

10. In your opinion, is the knowledge that underlies radically innovative / breakthrough drugs likely to come from other organizations / individuals or rather from the developing firm itself?
    a. Is such knowledge tacit or explicit?
    b. If the critical knowledge comes from outside the firm, how should a firm integrate it so that it can be transformed into an innovative / breakthrough drug?
        i. Can you think of any barriers for such knowledge integration?
    c. In your opinion, what would it take for pharmaceutical firms to develop a radically innovative / breakthrough drug that is based on a different technology or is related to another therapeutic class? **[note to interviewer: this question relates to RQ 3]**

11. Apparently, Bob Swanson [co-founder of Genentech] believed that Genentech's success was tied directly to creating an environment that enabled employees to do their best work. What they were setting out to do wouldn't be easy. Almost every day they would face hurdles and failures but would still have to persevere in pursuing goals that seemed out of reach. So, Genentech became famous for hosting their regular Friday afternoon social gatherings called "Ho-Hos."
    a. Do you have an image of specific firm values and believes that a company should have to be more likely to develop a radically innovative / breakthrough drug?
12. In your opinion, what role does a firm's management team play in the development of a radically innovative / breakthrough drug?

[Note to interviewer: questions linked to Research Question 3: How do inter-firm collaboration capabilities influence the radical drug innovation output of a firm?]

13. Roche acquired Syntex in 1994 [Syntex was a pioneering drug maker founded by scientists who invented the birth control pill in the 1950s. The company's fortunes rose quickly in the mid-1970s, when it unveiled its blockbuster drug naproxen]; mainly because of its promising drug candidates Cellcept and Valcyte. The research site in Palo Alto remained open and was integrated into the Roche R&D network. However, during the following 14 years the Palo Alto site could not deliver any new drug candidate. The Palo Alto site was eventually closed in 2010.
    a. In your opinion, is such an example of a failed acquisition rather an exception or is it common? Why?
14. Can you think of a scenario / context in which a R&D collaboration between pharmaceutical firms or a pharmaceutical firm and a research university is fundamental for the development of a radically innovative / breakthrough drug?

Closing

- Do you have any more comments or questions?
- What do you think? Was this a good use of your time?
- Can you recommend other experts that you think have knowledge about this topic and might be interested in participating in this research?
- I might contact you again to validate if my interpretations of the interview data is aligned with what you wanted to say.
- Thanks!
- **[Stop recording]**

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