Management Review Quarterly
https://doi.org/10.1007/s11301-021-00218-9

Determinants of radical drug innovation: a systematic literature review

Ingo Stiller[1,2] · Arjen van Witteloostuijn[1,3] · Bart Cambré[1]

Received: 24 April 2020 / Accepted: 18 March 2021

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 4100 peer-reviewed journal articles and PhD theses, of which we included 38 in the narrative synthesis. To guide the review, we use Crossan and Apaydin's (J Manag Stud 47:1154–1191, 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.

The paper represents the author's personal opinion and does not necessarily reflect the views of F. Hoffmann – La Roche AG or its staff.

✉ Ingo Stiller
istiller@mailbox.org

[1] Antwerp Management School and University of Antwerp, Antwerp, Belgium

[2] F. Hoffmann – La Roche AG, Basel, Switzerland

[3] School of Business and Economics, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

Published online: 31 March 2021

Keywords Systematic literature review · Radical innovation · Pharmaceuticals

JEL Classification O310 · O320

1 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 twentieth 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) report that 58% 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 (a) to summarize the current state of the art in research on what makes a pharmaceutical firm deliver radical innovations and (b) to synthesize the identified determinants into a comprehensive conceptual framework. This is the first systematic literature review on this twofold 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.

2 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).

2.1 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).

2.1.1 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 2000 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.

2.1.2 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 US FDA (e.g., Dunlap et al. 2014; Fernald et al. 2017), or priority-reviewed[1] 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 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).

2.2 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 Fig. 1, Crossan and Apaydin (2010) identify three distinct

[1] Drugs with potentially important therapeutic benefits receive a priority review by the US FDA, while all other drugs receive a standard review (Sternitzke 2010).

Fig. 1 Grouping of firm-level determinants of innovation (Crossan and Apaydin 2010)

groups of firm-level determinants of innovation: leadership, managerial levers, and business processes, each of which we describe briefly below.

2.2.1 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.

2.2.2 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.

2.2.3 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 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 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 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 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 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 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, 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). 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.

2.3 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;

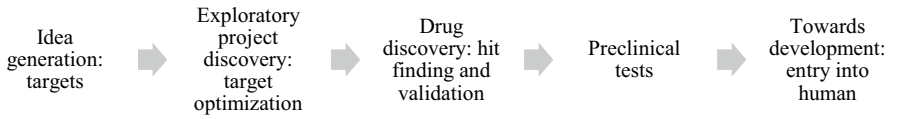

Fig. 2 Front-end innovation process in pharmaceutical research (Aagaard 2015)

Dubey and Dubey 2010; Munos 2009; Petrova 2014). Pharmaceutical firms invest, on average, about 15% 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 US 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% of all pharmaceutical products and 45% 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 US and the EMA in the EU. 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% 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 in Sect. 2.2.3 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 its R&D functional areas.

2.3.1 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 Fig. 2.

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.

2.3.2 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 3 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

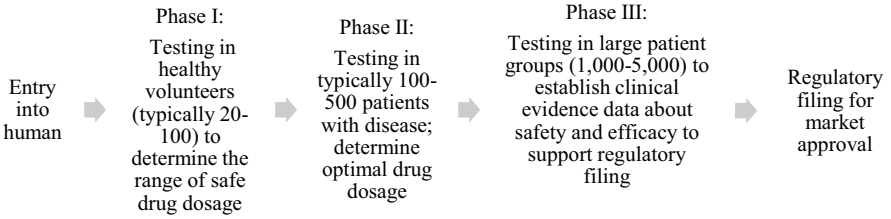

Fig. 3 Innovation process in pharmaceutical development (Petrova 2014)

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.

2.3.3 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 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

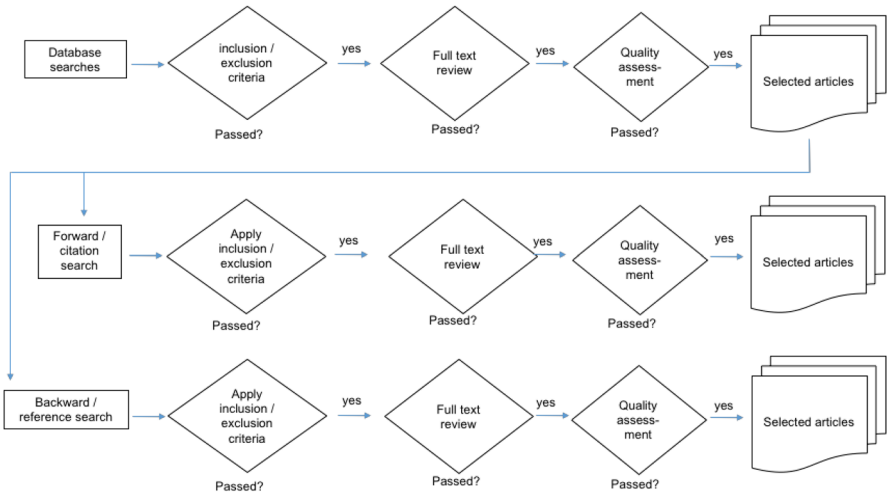

Fig. 4 Search strategy used for the systematic literature review

Table 1 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"))

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 Fig. 4 and detailed description below).

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 1).

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 2.

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 3, 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% agreement was reached. All papers with an average weighted score of 2.0 or higher were included in the final synthesis.

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:

Table 2 Criteria for screening papers

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)

Table 3 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

Table 4 A priori codes

1. Leadership (e.g., Bel 2010; Makri and Scandura 2010; van der Panne et al. 2003)
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-Jiménez 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)

(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 Sect. 2). These codes, shown in Table 4, 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

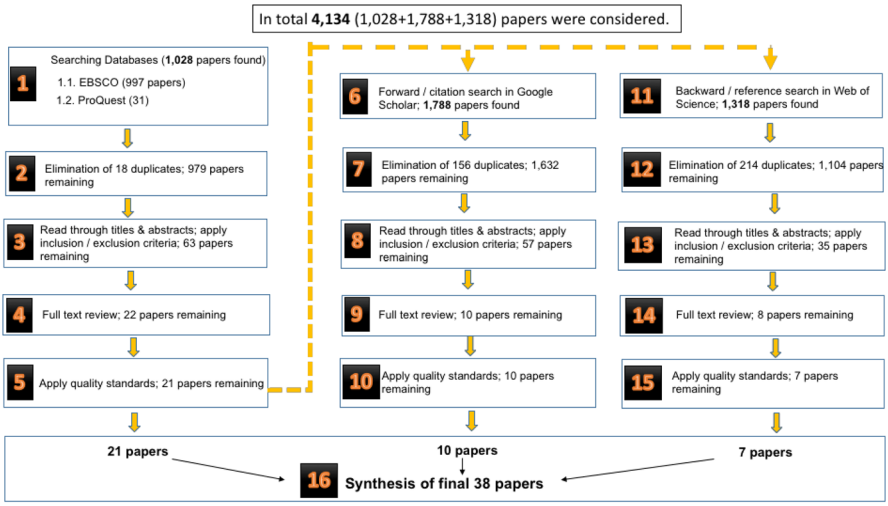

Fig. 5 Results of the systematic literature review screening process

Table 5 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)	1788	10	0.6
Backward search (Web of Science)	1318	7	0.5
Total	4134	38	0.9

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.

4 Results

Using the systematic literature review methodology described above, we considered 4134 peer-reviewed journal articles and PhD theses. Initial results from searches using EBSCO and ProQuest (Step 1 in Fig. 5) resulted in 1028 papers, given the rather broadly defined search string. The forward citation search also yielded a high number of citations: 1788 (Step 6 in Fig. 5), as did the backward reference search: 1318 (Step 11 in Fig. 5).

As shown in greater detail in Table 5, from the 4134 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 4134 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.

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 US, which is not surprising given that the US 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 6, 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.

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 6, 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).

Table 6 Definitions and measurement of radical innovation used in each paper

References	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		
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		

Table 6 (continued)

References	Determinants	Direction of relationship with radical drug innovation	Definition of radical innovation	Measurement of radical innovation
	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		
Dunlap et al. (2016)	R&D alliances	Positive	Scientific novelty	Joint NME and Priority Review count
	M&As	Negative		

Table 6 (continued)

References	Determinants	Direction of relationship with radical drug innovation	Definition of radical innovation	Measurement of radical innovation
Eslaminosratabadi (2018)[a]	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
Karamanos (2012)	R&D alliances (direct ties)	Curvilinear	The creation of technological knowledge that falls outside the firm's existing know-how	Patent count

Table 6 (continued)

References	Determinants	Direction of relationship with radical drug innovation	Definition of radical innovation	Measurement of radical innovation
	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)[a]	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		

Table 6 (continued)

References	Determinants	Direction of relationship with radical drug innovation	Definition of radical innovation	Measurement of radical innovation
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
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)[a]	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

Table 6 (continued)

References	Determinants	Direction of relationship with radical drug innovation	Definition of radical innovation	Measurement of radical innovation
	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		
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		

Table 6 (continued)

References	Determinants	Direction of relationship with radical drug innovation	Definition of radical innovation	Measurement of radical innovation
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

[a]PhD Thesis

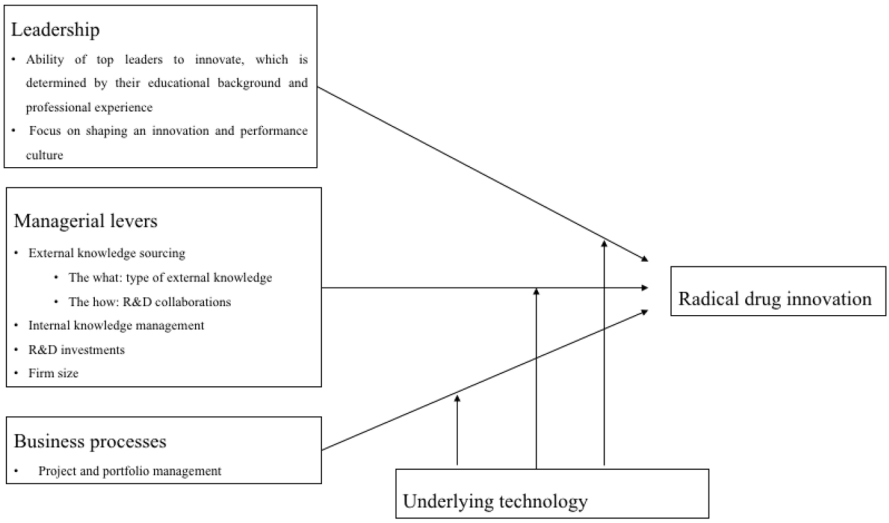

Fig. 6 Model for the determinants of radical drug innovation

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 US. 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).

5 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 6 displays the grouped determinants.

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 Fig. 6) to explore the potential moderating effect of technology on radical drug innovation over time.

5.1 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*.

5.1.1 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.

5.1.2 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.

5.2 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.

5.2.1 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.

5.2.1.1 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.

5.2.1.2 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.

5.2.2 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.

5.2.3 R&D investments

Each year, pharmaceutical companies around the globe invest in excess of 100 billion US 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% increases in R&D spending lead to 0.22% 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.

5.2.4 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.

5.3 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).

6 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 oversimplified 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 Fig. 2), 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 inhouse 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.

7 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 4100 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.

References

Aagaard A (2012) The contribution of innovation strategy development and implementation in active facilitation of pharmaceutical front end innovation. Syst Pract Action Res 25:457–477

Aagaard A (2015) Key differences and similarities in ways of managing and supporting radical pharmaceutical front end innovation: a case study of the pharmaceutical industry. Int J Innov Manag 19:155001
Aagaard A, Gertsen F (2011) Supporting radical front end innovation: perceived key factors of pharmaceutical innovation. Creativity Innov Manag 20:330–346
Academy of Management (n.d.) Reviewer Guidelines. http://aom.org/annualmeeting/reviewerguidelines. Accessed 28 Feb 2020
Achilladelis B (1993) The dynamics of technological innovation: the sector of antibacterial medicines. Res Policy 22:279–308. https://doi.org/10.1016/0048-7333(93)90001-X
Achilladelis B, Antonakis N (2001) The dynamics of technological innovation: the case of the pharmaceutical industry. Res Policy 30:535–588
Adams CP, Brantner VV (2006) Estimating the cost of new drug development: is it really $802 million? Health Aff 25:420–428
Ahuja G, Lampert CM (2001) Entrepreneurship in the large corporation: a longitudinal study of how established firms create breakthrough inventions. Strateg Manag J 22:521–543. https://doi.org/10.1002/smj.176
American Chemical Society International Historic Chemical Landmarks (1999) Discovery and development of Penicillin. Discovery and Development of Penicillin. http://www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html#alexander-fleming-penicillin. Accessed 28 Feb 2020
Andries P, Czarnitzki D (2014) Small firm innovation performance and employee involvement. Small Bus Econ 43:21–38
Arnold DG, Troyer JL (2016) Does increased spending on pharmaceutical marketing inhibit pioneering innovation? J Health Politics Policy Law 41:157
Bakhrebah MA, Nassar MS, Alsuabeyl MS, Zaher WA, Meo SA (2018) CRISPR technology: new paradigm to target the infectious disease pathogens. Eur Rev Med Pharmacol Sci 22:3448–3452
Bamberger P (2017) Construct validity research. Acad Manag Discov 3:235–238. https://doi.org/10.5465/amd.2017.0074
Baregheh A, Rowley J, Sambrook S (2009) Towards a multidisciplinary definition of innovation. Manag Decis 47:1323–1339. https://doi.org/10.1108/00251740910984578
Bel R (2010) Leadership and innovation: learning from the best. Glob Bus Organ Excell 29:47–60
Belderbos R, Gilsing VA, Suzuki S (2016) Direct and mediated ties to universities: "Scientific" absorptive capacity and innovation performance of pharmaceutical firms. Strateg Organ 14:32–52
Breznik L, Hisrich RD (2014) Dynamic capabilities vs. innovation capability: are they related? J Small Bus Enterp Dev 21:368–384
Bryman A, Bell E (2015) Business research methods. Oxford University Press
Büschgens T, Bausch A, Balkin DB (2013) Organizational culture and innovation: a meta-analytic review. J Prod Innov Manag 30:763–781
Buyl T, Boone C, Hendriks W, Matthyssens P (2011) Top management team functional diversity and firm performance: the moderating role of CEO characteristics. J Manag Stud 48:151–177
Camelo C, Fernández-Alles M, Hernández AB (2010) Strategic consensus, top management teams, and innovation performance. Int J Manpow 31:678–695
Cammarano A, Caputo M, Lamberti E, Michelino F (2017a) Open innovation and intellectual property: a knowledge-based approach. Manag Decis 55:1182–1208
Cammarano A, Michelino F, Caputo M (2017b) Enhancing innovation quality through the involvement of external partners: an explorative analysis on the bio-pharmaceutical industry. In: 2017 International Conference on Engineering, Technology and Innovation (ICE/ITMC). IEEE, Funchal, pp 324–334
Cardinal LB (2001) Technological innovation in the pharmaceutical industry: the use of organizational control in managing research and development. Organ Sci 12:19–36
Chandy RK, Tellis GJ (1998) Organizing for radical product innovation: the overlooked role of willingness to cannibalize. J Mark Res 35:474–487
Chesbrough H (2006) Open innovation: a new paradigm for understanding industrial innovation. In: Chesbrough H, Vanhaverbeke W, West J (eds) Open innovation: researching a new paradigm. Oxford University Press, Oxford, pp 1–12
Chiva R, Ghauri P, Alegre J (2014) Organizational learning, innovation and internationalization: a complex system model. Br J Manag 25:687–705

Claret J (2016) Organizing for breakthrough innovation. In: Organizing for breakthrough innovation. http://www.mckinsey.com/insights/innovation/Organizing_for_breakthrough_innovation. Accessed 28 Jan 2016

Cockburn IM (2004) The changing structure of the pharmaceutical industry. Health Aff 23:10–22. https://doi.org/10.1377/hlthaff.23.1.10

Cohen SK, Caner T (2016) Converting inventions into breakthrough innovations: the role of exploitation and alliance network knowledge heterogeneity. J Eng Technol Manag 40:29–44. https://doi.org/10.1016/j.jengtecman.2016.03.002

Cohen WM, Levinthal DA (1990) Absorptive capacity: a new perspective on learning and innovation. Admin Sci Q 35:128–152

Cohen LY, Kamienski PW, Espino RL (1998) Gate system focuses industrial basic research. Res Technol Manag 41:34–37

Cook DJ, Mulrow CD, Haynes RB (1997) Systematic reviews: synthesis of best evidence for clinical decisions. Ann Intern Med 126:376–380

Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G, Pangalos MN (2014) Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat Rev Drug Discov 13:419–431

Cooper RG (1994) Third-generation new product processes. J Prod Innov Manag 11:3–14

Crossan MM, Apaydin M (2010) A multi-dimensional framework of organizational innovation: a systematic review of the literature. J Manag Stud 47:1154–1191

Cucculelli M (2018) Firm age and the probability of product innovation. Do CEO tenure and product tenure matter? J Evol Econ 28:153–179

Curado C (2006) The knowledge based-view of the firm: from theoretical origins to future implications. Int J Learn Intellect Cap 3:367–381

Daellenbach US, McCarthy AM, Schoenecker TS (1999) Commitment to innovation: the impact of top management team characteristics. R&D Manag 29:199–208

Danneels E, Kleinschmidtb EJ (2001) Product innovativeness from the firm's perspective: its dimensions and their relation with project selection and performance. J Prod Innov Manag 18:357–373

De Man AP, Duysters G (2005) Collaboration and innovation: a review of the effects of mergers, acquisitions and alliances on innovation. Technovation 25:1377–1387

de Solà-Morales O, Cunningham D, Flume M, Overton PM, Shalet N, Capri S (2018) Defining innovation with respect to new medicines: a systematic review from a payer perspective. Int J Technol Assess Health Care 34:224–240

DiMasi JA (2000) New drug innovation and pharmaceutical industry structure: trends in the output of pharmaceuttical firms. Drug Inf J 34:1169–1194

Dubey J, Dubey R (2010) Pharmaceutical innovation and generic challenge: recent trends and causal factors. Int J Pharm Healthc Mark 4:175–190

Dunlap D, Marion T, Friar J (2014) The role of cross-national knowledge on organizational ambidexterity: a case of the global pharmaceutical industry. Manag Learn 45:458–476. https://doi.org/10.1177/1350507613480099

Dunlap D, McDonough EF, Mudambi R, Swift T (2016) Making up is hard to do: knowledge acquisition strategies and the nature of new product innovation. J Prod Innov Manag 33:472–491. https://doi.org/10.1111/jpim.12298

Dunlap-Hinkler D, Kotabe M, Mudambi R (2010) A story of breakthrough versus incremental innovation: corporate entrepreneurship in the global pharmaceutical industry. Strateg Entrep J 4:106–127. https://doi.org/10.1002/sej.86

Du Preez ND, Louw L (2008) A framework for managing the innovation process. In: PICMET '08-2008 Proceedings of the Portland International Conference on Management of Engineering & Technology

Elenkov DS, Manev IM (2005) Top management leadership and influence on innovation: the role of sociocultural context. J Manag 31:381–402

Eslaminosratabadi H (2018) The timing and type of alliance partnerships in the new product development process. Dissertation, McMaster University

Eveleens C (2010) Innovation management: a literature review of innovation process models and their implications. Science 800:900–916

Fagerberg J, Mowery DC, Nelson RR (2005) The Oxford handbook of innovation. Oxford University Press

Fernald K, Pennings H, Van Den Bosch J, Commandeur H, Claassen E (2017) The moderating role of absorptive capacity and the differential effects of acquisitions and alliances on Big Pharma firms' innovation performance. PLoS ONE 12:e0172488
Forés B, Camisón C (2016) Does incremental and radical innovation performance depend on different types of knowledge accumulation capabilities and organizational size? J Bus Res 69:831–848
Fosfuri A, Tribo J (2008) Exploring the antecedents of potential absorptive capacity and its impact on innovation performance. Omega 36:173–187. https://doi.org/10.1016/j.omega.2006.06.012
García-Morales VJ, Llorens-Montes FJ, Verdú-Jover AJ (2006) Antecedents and consequences of organizational innovation and organizational learning in entrepreneurship. Ind Manag Data Syst 106:21–42
García-Morales VJ, Llorens-Montes FJ, Verdú-Jover AJ (2008) The effects of transformational leadership on organizational performance through knowledge and innovation. Br J Manag 19:299–319
Gassmann O, Schweitzer F (2014) Management of the fuzzy front end of innovation. Springer, New York
Gatignon H, Tushman ML, Smith W, Anderson P (2002) A structural approach to assessing innovation: construct development of innovation locus, type, and characteristics. Manag Sci 48:1103–1122
Gerth AB (2013) How newly appointed chief information officers take charge: exploring the dynamics of leader socialization. Thesis, Cranfield University
Gilsing V, Nooteboom B (2006) Exploration and exploitation in innovation systems: the case of pharmaceutical biotechnology. Res Policy 35:1–23
Gittelman M (2016) The revolution re-visited: clinical and genetics research paradigms and the productivity paradox in drug discovery. Res Policy 45:1570–1585. https://doi.org/10.1016/j.respol.2016.01.007
Green SG, Gavin MB, Aiman-Smith L (1995) Assessing a multidimensional measure of radical technological innovation. IEEE Trans Eng Manag 42:203–214
Guevara HH, Soriano FH, Tuebke A, Vezzani A, Dosso M, Amoroso S, Grassano N, Coad A, Gkotsis P (2015) The 2015 EU Industrial R&D Investment Scoreboard (No. JRC98287). Joint Research Centre (Seville site)
Hakkarainen K, Talonen T (2014) The innovation funnel fallacy. Int J Innov Sci 6:63–72
Hall BH, Moncada-Paternò-Castello P, Montresor S, Vezzani A (2016) Financing constraints, R&D investments and innovative performances: new empirical evidence at the firm level for Europe. Econ Innov New Technol 25:1–14
Hambrick DC, Mason PA (1984) Upper echelons: the organization as a reflection of its top managers. Acad Manag Rev 9:193–206
Herstatt C, Verworn B (2001) The "fuzzy front end" of innovation. Working Paper, No. 4, Hamburg University of Technology (TUHH), Institute for Technology and Innovation Management (TIM), Hamburg
Hohberger J (2016) Does it pay to stand on the shoulders of giants? An analysis of the inventions of star inventors in the biotechnology sector. Res Policy 45:682–698
Hornke M, Mandewirth S (2010) Merger & acquisitions (M & A) in the pharmaceutical industry: the wheel keeps on turning. J Bus Chem 7:67–68
Horrobin DF (2000) Innovation in the pharmaceutical industry. J R Soc Med 93:341
Jiménez-Jiménez D, Sanz-Valle R (2011) Innovation, organizational learning, and performance. J Bus Res 64:408–417
Jong S, Slavova K (2014) When publications lead to products: the open science conundrum in new product development. Res Policy 43:645–654. https://doi.org/10.1016/j.respol.2013.12.009
Kahn KB (2018) Understanding innovation. Bus Horiz 61:453–460
Kamuriwo DS, Baden-Fuller C, Zhang J (2017) Knowledge development approaches and breakthrough innovations in technology-based new firms. J Prod Innov Manag 34:492–508. https://doi.org/10.1111/jpim.12393
Kanter RM (1983) The change masters: innovation for productivity in the American corporation. Simon and Schuster, New York
Karamanos AG (2012) Leveraging micro- and macro-structures of embeddedness in alliance networks for exploratory innovation in biotechnology. R&D Manag 42:71–89. https://doi.org/10.1111/j.1467-9310.2011.00664.x
Karamanos AG (2014) Exploratory and exploitative innovation performance contingent on alliance ego-network patterns. IJIRD 5:547. https://doi.org/10.1504/IJIRD.2014.066581

Karamanos AG (2016) Effects of a firm's and their partners' alliance ego-network structure on its innovation output in an era of ferment: networks for innovation during ferment. R&D Manag 46:261–276. https://doi.org/10.1111/radm.12163
Kennedy I (2009) Appraising the value of innovation and other benefits: a short study for London. NICE 246
Keyrouz R (2013) Is market orientation a driver for 'radical innovation'? An insight from the pharmaceutical industry. Available at SSRN: https://ssrn.com/abstract=3338899 or https://doi.org/10.2139/ssrn.3338899
Kitchenham B (2004) Procedures for performing systematic reviews. Keele University, United Kingdom
Kneller R (2010) The importance of new companies for drug discovery: origins of a decade of new drugs. Nat Rev Drug Discov 9:867–882. https://doi.org/10.1038/nrd3251
Kock A, Gemünden GH (2016) Antecedents to decision-making quality and agility in innovation portfolio management. J Prod Innov Manag 33:670–686
Koen PA (2004) The fuzzy front end for incremental, platform, and breakthrough products. In: PDMA Handbook of New Product Development, pp 81–91
Kotsemir M, Meissner D (2013) Conceptualizing the innovation process—trends and outlook. MPRA Paper 46504
Kovacs A, Marullo C, Verhoeven D, Van Looy B (2019) Radical, disruptive, discontinuous and breakthrough innovation: more of the same? Acad Manag Proc 2019:14866
Kremer M (2002) Pharmaceuticals and the developing world. J Econ Perspect 16:67–90
Lazzeri F, Pisano GP (2014) The organizational and geographic drivers of absorptive capacity: an empirical analysis of pharmaceutical R&D laboratories. Harvard Business School Technology & Operations Mgt. Unit Working Paper No. 14-098, Available at SSRN: https://ssrn.com/abstract=2423341
Lin C, Lin P, Song FM, Li C (2011) Managerial incentives, CEO characteristics and corporate innovation in China's private sector. J Comp Econ 39:176–190
Makri M, Scandura TA (2010) Exploring the effects of creative CEO leadership on innovation in high-technology firms. Leadersh Q 21:75–88
Malva AD, Kelchtermans S, Leten B, Veugelers R (2015) Basic science as a prescription for breakthrough inventions in the pharmaceutical industry. J Technol Transf 40:670–695. https://doi.org/10.1007/s10961-014-9362-y
Matzler K, Schwarz E, Deutinger N, Harms R (2008) The relationship between transformational leadership, product innovation and performancein SMEs. J Small Bus Entrep 21:139–151
McDermott CM, O'Connor GC (2002) Managing radical innovation: an overview of emergent strategy issues. J Prod Innov Manag 19:424–438
Mestre-Ferrandiz J, Sussex J, Towse A (2012) The R&D cost of a new medicine. Monographs, Office of Health Economics, number 000135
Midgley DF, Dowling GR (1978) Innovativeness: the concept and its measurement. J Consum Res 4:229–242
Mikkola JH (2001) Portfolio management of R&D projects: implications for innovation management. Technovation 21:423–435
Mohs RC, Greig NH (2017) Drug discovery and development: role of basic biological research. Alzheimers Dement Trans Res Clin Interv 3:651–657
Morgan S, Lopert R, Greyson D (2008) Toward a definition of pharmaceutical innovation. Open Med 2:e4
Morgan P, Brown DG, Lennard S, Anderton MJ, Barrett JC, Eriksson U, Fidock M, Hamren B, Johnson A, March RE, Matcham J, Pangalos MN (2018) Impact of a five-dimensional framework on R&D productivity at AstraZeneca. Nat Rev Drug Discov 17:167–181
Munos B (2009) Lessons from 60 years of pharmaceutical innovation. Nat Rev Drug Discov 8:959–968
Munos BH, Chin WW (2011) How to revive breakthrough innovation in the pharmaceutical industry. Sci Transl Med 3:89cm16. https://doi.org/10.1126/scitranslmed.3002273
Naranjo-Valencia JC, Jiménez-Jiménez D, Sanz-Valle R (2011) Innovation or imitation? The role of organizational culture. Manag Decis 49:55–72
Nicholas J (2014) An investigation into the practices and underlying factors during the fuzzy front end of radical innovation. Thesis, University of Limerick
O'Connor GC (2008) Major innovation as a dynamic capability: a systems approach. J Prod Innov Manag 25:313–330
OECD/Eurostat (2019) Oslo Manual 2018: guidelines for collecting, reporting and using data on innovation, 4th edn. OECD Publishing, Paris. https://doi.org/10.1787/9789264304604-en

Office for National Statistics (2015) How has life expectancy changed over time? How has life expectancy changed over time? https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/articles/howhaslifeexpectancychangedovertime/2015-09-09. Accessed 24 Nov 2019

Oskarsson G (2003) The antecedents and process of innovation. Paper presented at the IV Conference in Social Sciences, Reykjavík

Park HD, Tzabbar D (2016) Venture capital, CEOs' sources of power, and innovation novelty at different life stages of a new venture. Organ Sci 27:336–353. https://doi.org/10.1287/orsc.2016.1054

Pavitt K (2005) Innovation processes. In: Fagerberg J, Mowery D, Nelson RR (eds) The Oxford handbook of innovation. Oxford University Press, Oxford

Petrova E (2014) Innovation in the pharmaceutical industry: the process of drug discovery and development. In: Innovation and marketing in the pharmaceutical industry. Springer, New York, pp 19–81

Phene A, Fladmoe-Lindquist K, Marsh L (2006) Breakthrough innovations in the US biotechnology industry: the effects of technological space and geographic origin. Strat Manag J 27:369–388. https://doi.org/10.1002/smj.522

Pieterse AN, van Knippenberg D, Schippers M, Stam D (2010) Transformational and transactional leadership and innovative behavior: the moderating role of psychological empowerment. J Organ Behav 31:609–623

Qi Dong J, McCarthy KJ, Schoenmakers WW (2017) How central is too central? Organizing interorganizational collaboration networks for breakthrough innovation. J Prod Innov Manag 34:526–542

Quintana-García C, Benavides-Velasco CA (2011) Knowledge organisation in R&D alliances: its impact on product innovation. Technol Anal Strateg Manag 23:1047–1061. https://doi.org/10.1080/09537325.2011.621300

Régnier S (2013) What is the value of 'me-too' drugs? Healthc Manag Sci 16:300–313. https://doi.org/10.1007/s10729-013-9225-3

Reid SE, De Brentani U (2004) The fuzzy front end of new product development for discontinuous innovations: a theoretical model. J Prod Innov Manag 21:170–184

Rice M, Kelley D, Peters L, Colarelli O'Connor G (2001) Radical innovation: triggering initiation of opportunity recognition and evaluation. R D Manag 31(4):409–420

Ritter T, Gemünden HG (2004) The impact of a company's business strategy on its technological competence, network competence and innovation success. J Bus Res 57:548–556

Romasanta AKS, van der Sijde P, van Muijlwijk-Koezen J (2020) Innovation in pharmaceutical R&D: mapping the research landscape. Scientometrics 125:1801–1832

Rothwell R (1992) Successful industrial innovation: dritical factors for the 1990s. R D Manag 22:221–240

Rousseau DM, Wade-Benzoni KA (1994) Linking strategy and human resource practices: how employee and customer contracts are created. Human Resour Manag 33:463–489

Sampson RC (2007) R&D alliances and firm performance: the impact of technological diversity and alliance organization on innovation. Acad Manag J 50:364–386

Schuhmacher A, Germann PG, Trill H, Gassmann O (2013) Models for open innovation in the pharmaceutical industry. Drug Discov Today 18:1133–1137

Schuhmacher A, Gassmann O, Hinder M (2016) Changing R&D models in research-based pharmaceutical companies. J Transl Med 14:105

Schuhmacher A, Gassmann O, McCracken N, Hinder M (2018) Open innovation and external sources of innovation. An opportunity to fuel the R&D pipeline and enhance decision making? J Transl Med 16:119

Sharifirad MS, Ataei V (2012) Organizational culture and innovation culture: exploring the relationships between constructs. Leadersh Organ Dev J 33:494–517

Shefer D, Frenkel A (2005) R&D, firm size and innovation: an empirical analysis. Technovation 25:25–32

Singh J, Fleming L (2010) Lone inventors as sources of breakthroughs: myth or reality? Manag Sci 56:41–56

Slater SF, Mohr JJ, Sengupta S (2014) Radical product innovation capability: literature review, synthesis, and illustrative research propositions. J Prod Innov Manag 31:552–566

Smith M, Busi M, Ball P, Van der Meer R (2008) Factors influencing an organisation's ability to manage innovation: a structured literature review and conceptual model. Int J Innov Manag 12:655–676

Sorescu AB, Chandy RK, Prabhu JC (2003) Sources and financial consequences of radical innovation: insights from pharmaceuticals. J Mark 67:82–102

Stefanovska Ceravolo L, Polenakovik R, Dzidrov M (2016) Summary of innovation models on a company level—creating a framework for an innovation model that will increase a company's innovation activity. Int Sci J Bus Soc 1:22–26
Sternitzke C (2010) Knowledge sources, patent protection, and commercialization of pharmaceutical innovations. Res Policy 39:810–821
Stiller I, van Witteloostuijn A, Cambré B (2020) Do current radical innovation measures actually measure radical drug innovation? Scientometrics 126:1049–1078
Supriyadi F (2013) The influence of strategic leadership on firm inventive and innovative performance. Dissertation, University of Pittsburgh
Suzuki O (2018) Enabling or constraining? Unraveling the influence of organizational slack on innovation. Ind Corp Chang 27:555–575
Suzuki O, Methe DT (2014) Local search, exploration frequency, and exploration valuableness: evidence from new pharmaceuticals development. Int J Innov Mgt 18:1450014. https://doi.org/10.1142/S1363919614500145
Teece DJ, Pisano G, Shuen A (1997) Dynamic capabilities and strategic management. Strat Manag J 18:509–533
Thorpe R, Holt R, Macpherson A, Pittaway L (2005) Using knowledge within small and medium-sized firms: a systematic review of the evidence. Int J Manag Rev 7:257–281
Tidd J (2006) A review of innovation models. Discussion paper, Imperial College London, 1–16
Tranfield D, Denyer D, Smart P (2003) Towards a methodology for developing evidence-informed management knowledge by means of systematic review. Br J Manag 14:207–222
Tushman ML, Anderson P (1986) Technological discontinuities and organizational environments. Adm Sci Q 31:439–465
Tzabbar D, Margolis J (2017) Beyond the startup stage: the founding team's human capital, new venture's stage of life, founder–ceo duality, and breakthrough innovation. Organ Sci 28:857–872. https://doi.org/10.1287/orsc.2017.1152
van der Panne G, Van Beers C, Kleinknecht A (2003) Success and failure of innovation: a literature review. Int J Innov Manag 7:309–338
Van Norman GA (2016) Drugs, devices, and the FDA: part 1: an overview of approval processes for drugs. JACC Basic Transl Sci 1:170–179
van Witteloostuijn A (2016) What happened to Popperian falsification? Publishing neutral and negative findings. Cross Cult Strateg Manag 23:481–508
Vanhaverbeke W, Peeters N (2005) Embracing innovation as strategy: corporate venturing, competence building and corporate strategy making. Creativity Innov Manag 14:246–257
Wang C, Luxhøj JT, Johansen J (2004) Applying a knowledge management modeling tool for manufacturing vision (MV) development. Ind Manag Data Syst 104:735–743
Wang G, Holmes RM Jr, Oh IS, Zhu W (2016) Do CEOs matter to firm strategic actions and firm performance? A meta-analytic investigation based on upper echelons theory. Pers Psychol 69:775–862
Watts AD, Hamilton RD (2013) Scientific foundation, patents, and new product introductions of biotechnology and pharmaceutical firms. R&D Manag 43:433–446. https://doi.org/10.1111/radm.12023
Wuyts S, Dutta S, Stremersch S (2004) Portfolios of interfirm agreements in technology-intensive markets: consequences for innovation and profitability. J Mark 68:88–100. https://doi.org/10.1509/jmkg.68.2.88.27787
Xu S (2015) Balancing the two knowledge dimensions in innovation efforts: an empirical examination among pharmaceutical firms. J Prod Innov Manag 32:610–621
Xu S, Kesselheim AS (2014) Medical innovation then and now: perspectives of innovators responsible for transformative drugs. J Law Med Ethics 42:564–575
Xu S, Wu F, Cavusgil E (2013) Complements or substitutes? Internal technological strength, competitor alliance participation, and innovation development. J Prod Innov Manag 30:750–762. https://doi.org/10.1111/jpim.12014
Yadav MS, Prabhu JC, Chandy RK (2007) Managing the future: CEO attention and innovation outcomes. J Mark 71:84–101
Yeoh P-L, Roth K (1999) An empirical analysis of sustained advantage in the U.S. pharmaceutical industry: impact of firm resources and capabilities. Strateg Manag J 20:637–653
Zheng Y, Yang H (2015) Does familiarity foster innovation? The impact of alliance partner repeatedness on breakthrough innovations. J Manag Stud 52:213–230. https://doi.org/10.1111/joms.12112

Zucker LG, Darby MR, Armstrong JS (2002) Commercializing knowledge: university science, knowledge capture, and firm performance in biotechnology. Manag Sci 48:138–153. https://doi.org/10.1287/mnsc.48.1.138.14274