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Do current radical innovation measures actually measure radical drug innovation?

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Abstract

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

Keywords Radical innovation · Measurement · Health technology assessment · Pharmaceuticals

Introduction

A large and growing body of literature focuses on the antecedents, processes, and impacts of radical innovation within a range of environments. More than 170 scholarly papers with the term *radical innovation*[1] in the title were published in the short period

[1] Throughout this paper, the term *radical innovation* is used to describe rare and high-impact innovations, which provide competitive advantages to firms (Tushman and Anderson 1986). Other terms that are synonymous with *radical innovation* are breakthrough, major, and revolutionary innovations (Danneels and Kleinschmidt 2001).

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from January 2017 to January 2019[2] alone in journals such as *Research Policy, Journal of Knowledge Management, Academy of Management Proceedings, European Journal of Innovation Management, Journal of Organizational Change,* and *Public Management Review*. This suggests that radical innovations are a central and popular topic across a variety of fields such as organization studies, management science, and public policy (Fagerberg et al. 2005; Gopalakrishnan and Damanpour 1997; Hagedoorn and Cloodt 2003; Jiménez-Jimenez et al. 2008; Sorescu et al. 2003).

Studies on the topic of radical innovation have been carried out without full consideration or rigorous testing with regard to the definition and measurement of this critical concept. Indeed, it is challenging to define an innovation's radicalness because it is a theoretical construct, or an "unobservable property of objective reality" (Midgley and Dowling 1978, p. 230). Because radical innovations are abstract and latent, rather than concrete and directly observable, a careful definition and delineation of the construct is required prior to deciding how to measure it. However, the extant literature is replete with a diversity of definitions and, as a result, suffers notably from construct ambiguity. Relatedly, far too little attention has been paid to the development and validation of a standardized measurement of radical innovation. In fact, there is currently no commonly accepted measure of radical innovation (Dahlin and Behrens 2005; Green et al. 1995; Hagedoorn and Cloodt 2003; Verhoeven et al. 2016; Wang and Ahmed 2004).

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

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

[2] A Google Scholar search on 10 February 2019 resulted in 175 papers with *radical innovation* in the title that had been published since the beginning of 2017.

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

While there have been substantial efforts in prior studies to validate measures of radical inventions, particularly through patent-based measures (e.g., Dahlin and Behrens 2005; Kaplan and Vakili 2015; Verhoeven et al. 2016), there have been limited efforts to explicitly validate specific measures of radical *drug* innovation. As such, it remains unclear what exactly constitutes radical drug innovation, and whether current measures of radical drug innovation actually assess what they purport to measure (de Solà-Morales et al. 2018; Morgan et al. 2008). This undermines our ability to understand radical drug innovations, explain their antecedents, and demonstrate their implications for management and policymaking. Innovation scholars rely on these relatively untested measures to develop and examine their innovation theories. This calls into question the extent to which these developed theories (e.g., regarding the antecedents and outcomes of absorptive capacity[3]) are valid, given that they were tested in pharmaceutical environments with potentially inaccurate measures (e.g., Hohberger 2016; Malva et al. 2015; Phene et al. 2006; Suzuki and Methe 2014; Zucker et al. 2002).

Another challenge associated with these methodological issues is that they inhibit the comparison and integration of results across studies, hence impeding further advances on the topic. For example, while some research on radical drug innovation has concluded that smaller pharmaceutical companies deliver more radical innovations than larger ones (Yamin and Otto 2004), others have come to the opposite conclusion (e.g., Dunlap-Hinkler et al. 2010; Sorescu et al. 2003). Because each of these studies measured radical drug innovations differently, they do not provide a clear and consistent understanding of the relationship between pharmaceutical firm size and radical drug innovation, as is the case for much research in this area. Indeed, as noted by Bamberger (2017, p. 237), "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."

The current paper addresses the problem of radical drug innovation measurement, provides evidence of the limitations associated with the current state of the art, and offers a new measurement method based on the German health technology assessment (HTA) approach. HTA is an evidence-based process that compares the benefits and adverse effects of new drugs versus already existing drugs for the treatment of the same clinical condition (Panteli et al. 2015), thereby enabling physicians and payers to optimize healthcare treatments. These assessments help to ensure that finite public healthcare resources are effectively allocated to truly innovative drugs. Policymakers in an increasing number of

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

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countries (e.g., Canada, France, Germany, and the UK) have implemented HTA to determine the additional therapeutic value of new drugs versus existing ones (Ciani et al. 2016; Leverkus and Chuang-Stein 2016). However, HTA methods have not yet been broadly adopted by scholars to measure radical drug innovations in empirical research. The current research develops and validates a new measure of radical drug innovation based on HTA. This validated measure will improve comparability across studies, will help us better understand radical innovation within the industry and its impacts on outcomes, and, in turn, will stimulate further research.

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

Background

Radical innovation definitions and measurement issues

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

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

Researchers also vary in their conceptualization and assessment of incremental innovations. The major difference between radical and incremental innovations is the magnitude of novelty and the degree of customer need fulfillment. On the one hand, incremental innovations represent minor improvements, when compared to existing products, services, or processes across both dimensions, offering a marginal extra degree of need fulfillment.

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On the other hand, radical innovations symbolize major improvements and a large degree of extra need fulfillment in comparion to existing products, services, or processes. It is also important to highlight the important distinction between inventions and innovations, because some research is dedicated to radical inventions (e.g., Ahuja and Lampert 2001; Malva et al. 2015), while others analyze radical innovations (e.g., Arnold and Troyer 2016; Dunlap-Hinkler et al. 2010). An invention refers to a new idea or discovery (e.g., which could be patented), whereas an innovation goes beyond the invention, requiring commercial use of the invention (Kanter 1983). This difference has immediate implications for the radical invention and innovation constructs, as well as their measurement. The present paper focuses on radical *innovations*.

Radical drug innovation definition and measurement issues

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

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

Studies on radical drug innovation are plagued by relatively untested measures of the concept – not surprising, given the lack of definitional consensus. In their literature review, Kesselheim et al. (2013) identified four primary approaches to the measurement of radical drug innovation across 42 studies: drug/New Molecular Entities (NME) counts (21/42, 50%), therapeutic value (14/42, 33%), patents (4/42, 10%), and economic assessments (3/42, 7%). These different measurement methods have been used to capture radical drug innovation, but there have been limited efforts to validate them, let alone to evaluate their differences and similarities. The following sections include descriptions and limitations of these methods.

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Drug/NME counts

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

Following the FDA, NMEs can be further differentiated into first-in-class and follow-on drugs (US Food & Drug Administration 2020). A first-in-class drug is defined as a drug that uses—until then—a new and unique mechanism of action for treating a medical condition (Eder et al. 2014; Lexchin 2016). The term *drug class* describes drugs that are grouped together because of their similarities, such as their mechanism of action. The first drug that is based on a new mechanism of action is considered to be a first-in-class drug. However, there is some ambiguity in this approach. For example, a first-in-class drug can be either defined as a drug that uses a new mechanism of action for the first time, independent of any particular disease area, or as a drug that uses a new mechanism of action for a particular disease for the first time, even if the same mode of action was already used for the treatment of other diseases. Because of this ambiguity, researchers frequently examine drug innovation by using the NME method instead of the first-in-class classification, because the NME classification is thought to be unambiguous. Recent studies have categorized NME drugs as radically innovative and non-NME drugs as incrementally innovative (Cardinal and Hatfield 2000; Cohen and Caner 2016; Dunlap et al. 2013; Fernald et al. 2017).

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

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Patents

Patents are critical for pharmaceutical firms because they provide market exclusivity and, in turn, help to recoup the major R&D investments made in pursuit of new drugs. According to an analysis of the innovative activity of Europe's largest industrial firms, pharmaceutical companies file patents for approximately 80 per cent of their product innovations (Arundel and Kabla 1998). The common use of patents and their data availability in the public domain make them very attractive for empirical research within the pharmaceutical industry. More specifically, counts of both patent forward and patent backward citations[4] are frequently used in the literature to measure radical drug inventions (see Dahlin and Behrens 2005, for a comprehensive overview of patent-based measurement approaches). While forward patent citations are commonly used as a proxy for patent value and impact (Trajtenberg 1990), backward patent citations are understood to be a measure of novelty (Dahlin and Behrens 2005; Shane 2001). Prior studies have identified radical drug inventions based on patents within the top 1% (e.g., Ahuja and Lampert 2001), 2% (e.g., Hohberger 2016; Phene et al. 2006), or 5% (e.g., Singh and Fleming 2010) of the forward citations within the relevant patent class. Although patents are most frequently linked to drug inventions, some researchers have used patent-based indicators to assess radical drug innovations. For example, in their frequently cited paper, Phene et al. (2006) conceptualize radical innovations based on counts of patent citations.

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

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

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of the biological ingredient and for the tradename (which is extremely time-consuming and potentially error-prone) or purchase access to a commercial database, which is fairly expensive. Although many of the limitations of patent-based measures can be overcome, they reduce the practicality of research because they require context-specific adjustments in the data collection process.

Economic assessments

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

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

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

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

The second limitation of the QALY approach lies in the methodology for the adjustment of quality of life. There are different methods, such as the time trade-off (TTO) method,[5] for the quality adjustment, and it is well established that they lead to different QALY outcomes (Beresniak et al. 2015). Acknowledging the methodological limitations of the QALY approach, the European Commission funded the ECHOUTCOME research project to examine the validity of the QALY approach. The study, based on more than 1,300 respondents, could not validate the QALY method because there were important differences between the TTO preferences expressed by the respondents and the assumed TTO choices that are part of the QALY calculation (Beresniak et al. 2015).

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

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

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

Therapeutic value

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

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

While this two-dimensional operationalization of radical drug innovation is conceptually aligned with Chandy and Tellis (1998), who defined radical innovation through novelty and customer value, the operationalization of a new drug's therapeutic value through the FDA Priority Review characterization is potentially flawed. The FDA's Priority Reviews have important limitations, which are the same for the other Expedited Review programs (i.e., Fast Track, Accelerated Approval, and Breakthrough Therapy). First, the FDA uses expedited programs to review drug candidates that are believed (at the time of the submission of the drug application) to offer potentially important clinical improvements. However, there is no guarantee that these drug candidates actually provide therapeutic improvements after they are approved and used (Chary 2016; Darrow et al. 2020; Hwang et al. 2018). Second, recent evidence shows that FDA-expedited programs are, in general, approved on the basis of fewer and smaller clinical trials (Wallach et al. 2018). Drugs approved through Expedited Review programs are more likely to receive FDA safety actions later on (Wallach et al. 2018) because these drugs have higher incidences of safety issues post-approval (Pinnow et al. 2018), including increased incidences of serious adverse reactions (Olson 2008)

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and safety-related label changes after approval, particularly those representing highest risk warnings (Mostaghim et al. 2017). In summary, while the aim to more quickly bring potentially innovative drugs to patients in need is laudable, shorter review processes based on clinical trials with smaller patient populations lead to greater uncertainty about drug efficacy and safety. There is important evidence that FDA's Expedited Review programs may lead to the approval of drugs that carry greater risks than benefits. Thus, the use of any of these expedited programs as a single proxy of the additional therapeutic value of a new drug might be problematic.

Reconceptualization of an existing construct using health technology assessments

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

One solution to address this major limitation may come from utilizing a new, two-dimensional measure that is based on drug novelty, which is captured through the NME classification, and the additional therapeutic value of a drug, measured through Germany's HTA approach instead of Priority Reviews. The German HTA approach was chosen because it assesses the additional therapeutic value of new drugs based on clinical studies and does not use an approach based upon quality-adjusted life years (QALYs), which has been convincingly judged to be flawed by some researchers (see discussion above and de Solà-Morales et al. 2018; Leverkus and Chuang-Stein 2016).

Health technology assessment

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

HTA addresses this gap by identifying effective treatment options through the "systematic evaluation of properties, effects, and/or impacts of health technology" (WHO | HTA Definitions n.d.). HTA is an evidence-based process that examines the consequences of using a healthcare technology (e.g., a new drug or a new treatment procedure) by analyzing its associated medical, social, economic, and ethical issues (Panteli et al. 2015). More specifically, the HTA approach compares the benefits and adverse

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effects of alternative drugs for the treatment of the same clinical condition (Panteli et al. 2015), thereby enabling physicians and payers to optimize healthcare treatments. HTA may be based on examinations of clinical efficacy, safety, real-world effectiveness, and the social and ethical impacts of using the drug. Many countries (e.g., the UK) require cost-effectiveness assessments to be part of HTA in order to guide reimbursement and access decisions. The results from HTA are becoming increasingly recognized and considered when making health policy decisions in many countries (Panteli et al. 2015; Postma et al. 2011), including whether a new drug should be reimbursed by public healthcare systems and to predict which patients might benefit most from new drugs.

HTA was implemented in Germany in 2000 (Fricke and Dauben 2009). As part of the German HTA framework, clinical benefits assessments[6] of new drugs were made mandatory in the country in 2011 (Leverkus and Chuang-Stein 2016). This means that all new drugs must be evaluated against a comparator, typically the existing standard of care,[7] in order to assess the presence and magnitude of the new drug's additional clinical benefits (Schlette and Hess 2013). This assessment first includes an analysis of the pharmaceutical company's dossier by the German Institute for Quality and Efficiency in Healthcare (IQWiG). Subsequently, the Federal Joint Committee (G-BA), which is Germany's highest decision-making body of physicians, hospitals, and health insurance funds, makes final decisions with regard to the drug's added benefits (Schlette and Hess 2013).

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

Using NME and HTA to classify radical drug innovations

Before developing a new method to measure radical drug innovation, a careful definition and delineation of the construct is required. In their recent systematic literature review on the definitions of drug innovation, de Solà-Morales et al. (2018) found that drug innovation was most frequently characterized by the therapeutic value of drugs, followed by drug novelty. Building on this characterization, a new drug can be considered radically innovative (1) if it provides evidence for important additional therapeutic value (net of treatment risks) to patients when compared to already existing drugs that are intended to treat the same clinical condition and (2) if it is based on a new structure or mechanism of action.

6FL01 [6] Benefit assessment of pharmaceuticals in accordance with the German Social Code, Book Five (SGB V),
6FL02 Sect. 35a.

7FL01 [7] Guidelines, typically developed by a specialist society, that are generally accepted in the medical commu-
7FL02 nity for the treatment of a disease or condition.

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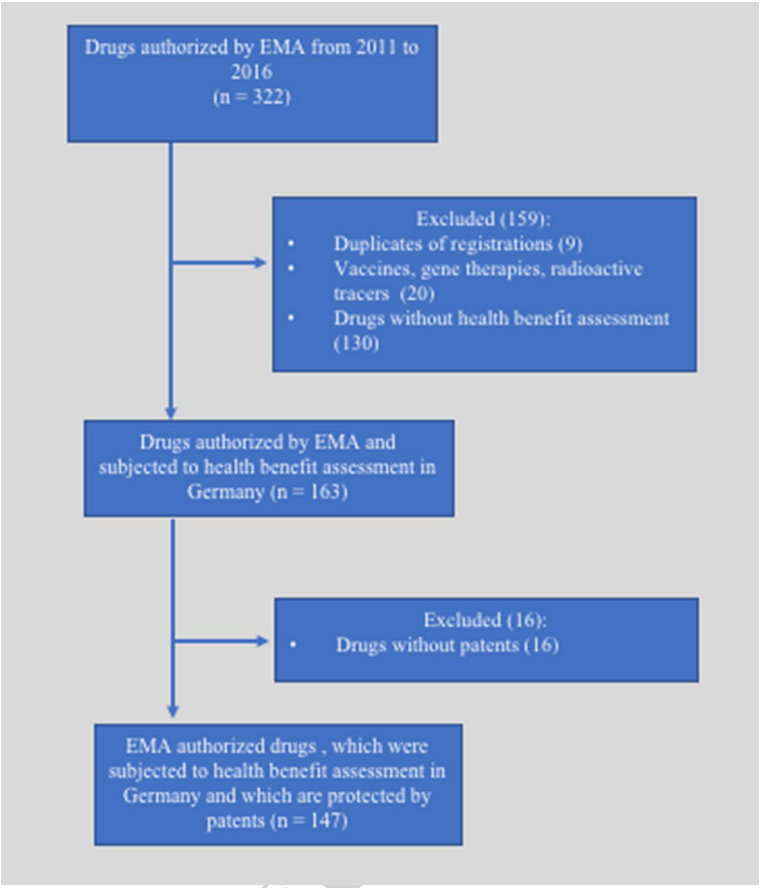

Fig. 1 Construction of the data set

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

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Data and methodology

Data

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

For these 147 drugs, additional information was collected from the approved drug product database of the FDA, such as the drugs' NDA classification codes and regulatory review types (priority versus standard; US Food & Drug Administration, n.d.-c), as well as the outcomes of the early benefit assessments from the database of the G-BA. All information for the patent-based analysis was taken either from the PATSTAT database (European Patent Office n.d.) or a commercial patent database (think Biotech LLC n.d.). Figure 1 summarizes the data collection process. Due to the recent implementation of the German HTA (early benefit assessment) in 2011, the size of the available data set is limited, and no sampling was performed.

Methodology

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

For the first measure (*Patent Top5*), following the approach proposed by Shane (2001) that was also described in the 2015 OECD working paper "Measuring the technological and economic value of patents" (OECD 2015) and by Dahlin and Behrens (2005), we assessed the radicalness of the 147 drugs using backward citation analysis. According to Shane (2001), an invention is more radical if its underlying patents cite more previous patents in patent classes that are different from the patent classes of the patents that protect the invention. The higher the ratio (between 0 and 1), the more radical the invention is: A radicalness index of 1 means that all patents of the invention cite previous patents that are all in patent classes that differ from the patent classes of the patents that protect the invention. We calculated the radicalness index for each focal patent, and for all other patents granted in the same year and in the same four-digit international patent class (IPC) as the focal

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patent. If a focal patent was within the top 5 per cent of the Shane radicalness index within the relevant four-digit IPC patent class from the same year in which the focal patent was approved, then we classified the drug as radically innovative, and otherwise as incrementally innovative. We chose the 5 per cent cutoff point because it had been used in previous research (e.g., Singh and Fleming 2010).

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

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

Finally, the innovativeness of the 147 drugs was assessed using the newly developed measure based on NMEs and the German HTA (*NME + HTA*[8]). All biologics and all NMEs that also carried a designation of a major or considerable additional clinical benefit were categorized as radically innovative. All others were classified as incrementally innovative. Table 2 provides an overview of all measurement methods used in this study.

Results

Measuring drug innovativeness through current measures

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

The two current measures of novelty (*NME* and *Patent Top5*), when compared to the current measure based on novelty and therapeutic value (*NME + Priority Review*), come with considerably different outcomes as well. As can be seen from the data in Table 4, only 69 (55%) of the 126 drugs that are classified as radically innovative using the *NME*

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

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

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

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

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

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

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

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

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

only approach are also categorized as such by the *NME + Priority Review* method. The difference in the outcomes between *Patent Top5* and *NME + Priority Review* are even more notable. As shown in Table 5, only 26 (38%) of the 69 drugs that are classified as radically

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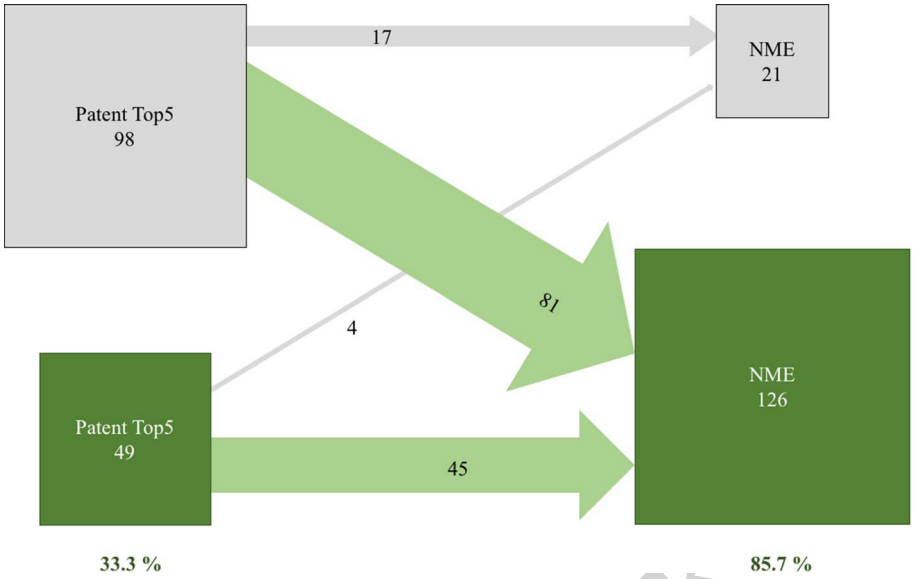

Fig. 2 Differences in outcomes between *Patent Top5* and *NME* (Sankey diagram)

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

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

innovative using the *NME + Priority Review* approach are also categorized as such by the *Patent Top5* only method.

The Sankey diagrams shown in Fig. 2 through 4 aim to better visualize the differences in outcomes between the different measurement models. Radically innovative drugs are depicted in green boxes, and drugs characterized as incrementally innovative are shown in gray boxes. The size of the boxes and arrows is based on the number of drugs in each category. As can be seen in Fig. 2, out of the total 147 drugs, 49 (33%) are categorized as radical drug innovations based on the *Patent Top5* measure, and 126 (86%) as radical drug innovations based on the *NME* measure. From the 98 drugs classified as incremental drug innovations through the *Patent Top5* method, 81 (83%) are

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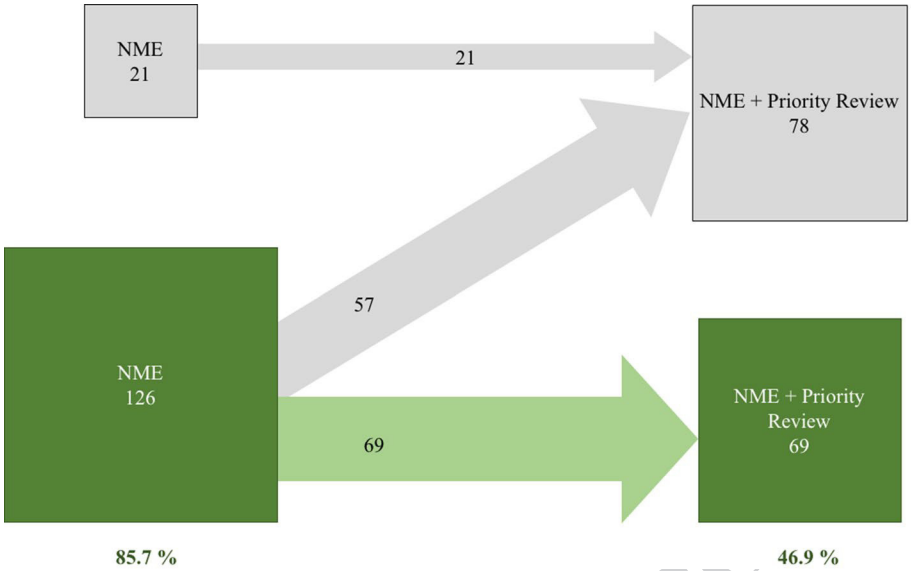

Fig. 3 Differences in outcomes between *NME* and *NME + Priority Review* (Sankey diagram)

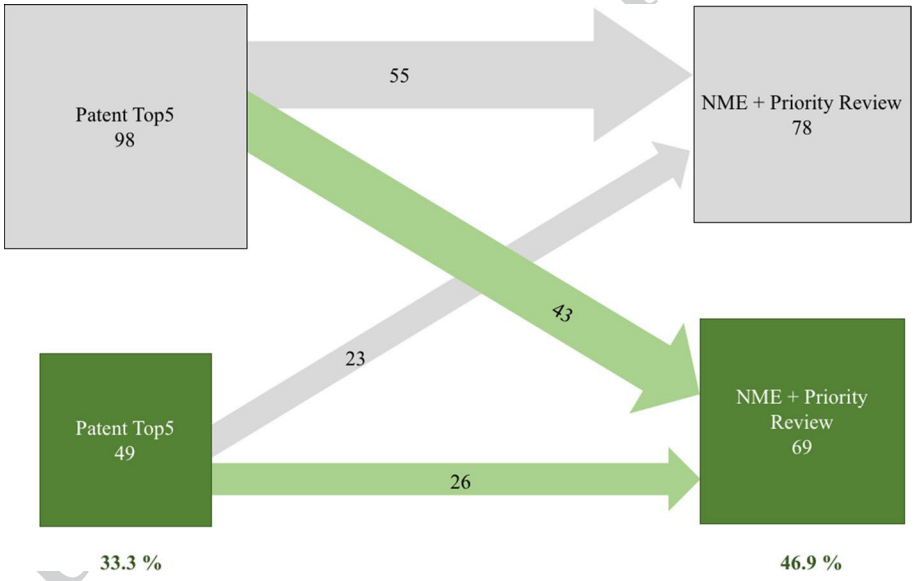

Fig. 4 Differences in outcomes between *Patent Top5* and *NME + Priority Review* (Sankey diagram)

categorized as radical drug innovations and only 17 (17%) as incremental innovations through the *NME* method. The Sankey diagrams visualize the very inconsistent measurement outcomes of the three current measures of radical drug innovation: The measures do not seem to assess the same concept.

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Measuring the radicalness of innovations using the HTA approach

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

Two cases

Two cases out of the 147 drugs in the sample are presented below to highlight the outcomes associated with the various measurement approaches that were examined above. Both are typical cases because they represent drugs that got approved by the regulatory authority (FDA) based on clinical trials showing the drugs to be safe and effective in treating the clinical condition of the patient population. As discussed above, to obtain approval from the FDA, it was not necessary to provide evidence of clinical superiority of the new drugs versus already available treatment options. The two cases presented below—regorafenib and trametinib—highlight differences in measurement outcomes. (Figs. 3, 4)

Regorafenib (trade name: Stivarga®) was approved in 2012 by the FDA (US Food & Drug Administration 2012) and in 2013 by the EMA (European Medicines Agency 2013) for the treatment of metastatic colorectal cancer based on the results of the phase 3 CORRECT trial, which showed statistically significant increases in both overall survival (OS) and progression-free survival (PFS) when compared to placebo (US National Library of Medicine 2015). However, in real-world terms, the median overall survival benefit of 45 days was rather modest, and important toxic effects (54% versus 14% in the placebo group) were observed in the trial population (Scheithauer 2012).

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

The FDA categorized Stivarga® as an NME because its active ingredient, regorafenib, had not been previously marketed in the US. Moreover, the FDA chose to do a Priority Review of the drug application because regorafenib treats a serious condition and could provide significantly improved effectiveness based on the phase 3 CORRECT trial. Thus, when the innovativeness of this drug is assessed using the current approaches of either novelty alone (*NME*) or novelty plus therapeutic value (*NME + Priority Review*), it is classified as a radical innovation.

The mandatory benefit assessment of Stivarga® in Germany in 2013 resulted in a *minor additional benefit* rating for patients suffering from metastatic colorectal cancer when compared to the current best supportive care (Gemeinsamer Bundesausschuss 2016a). This is

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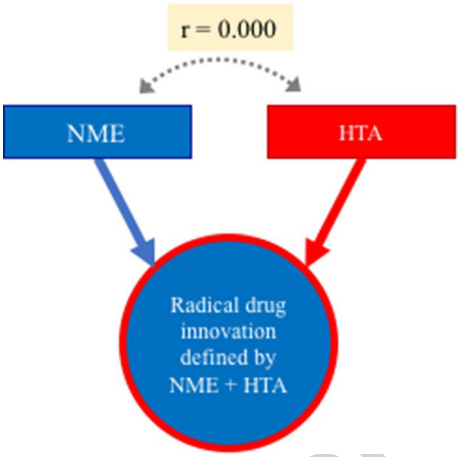

Fig. 5 Formative measure of radical drug innovation (*NME + HTA*)

Table 7 Correlations between *NME and HTA*

NME	*HTA*
Pearson Correlation	0.000
Sig. (2-tailed)	1.000
N	147

because the modest gain in median overall survival of 45 days was considered to be partially offset by the additional negative side effect (toxicity) and its impact on the overall quality of life of patients suffering from metastatic colorectal cancer. Hence, when applying the newly developed measure that incorporates the HTA approach (*NME + HTA*), the drug gets categorized as an incremental innovation.

Trametinib (trade name: Mekinist®) was approved by the FDA in 2013 (US Food & Drug Administration 2013) and by the EMA in 2014 (European Medicines Agency 2014) for the treatment of unresectable or metastatic melanoma in adult patients based on the results of the phase 3 METRIC trial, which compared Mekinist® versus chemotherapy (US National Library of Medicine 2018). The primary outcome measure of the trial was progression-free survival (PFS), which is a surrogate endpoint. The trial results showed a statistically significant increase in PFS for patients treated with Mekinist®; the median PFS was 4.9 months versus 1.5 months in the chemotherapy group.

Mekinist® is protected by eight US patents (7378423, 8580304, 8835443, 8703781, 9155706, 9271941, 8952018, and 9399021). Based on our backward citation analysis, the radicalness indexes of these patents ranged from 0.07 (patent 8835443) to 0.61 (patent 8952018), but none of the focal patents were within the top 5 per cent of the radicalness index within the relevant four-digit IPC patent classes (A61J, A61K, A61P, C07D, C07C, C07F) from the same year in which the focal patents were approved. Consequently, Mekinist® qualifies only as an incremental drug innovation based on the backward patent citation metric. AQ1

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

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

	Unstandardized coefficients		*Standardized coefficients*		
Model	*B*	*Std. Error*	*Beta*	*t*	*Sig*
(Constant)	−0.204	0.034		−6.076	0.000
1					
NME	0.238	0.035	0.207	6.708	0.000
HTA	0.857	0.029	0.906	29.394	0.000

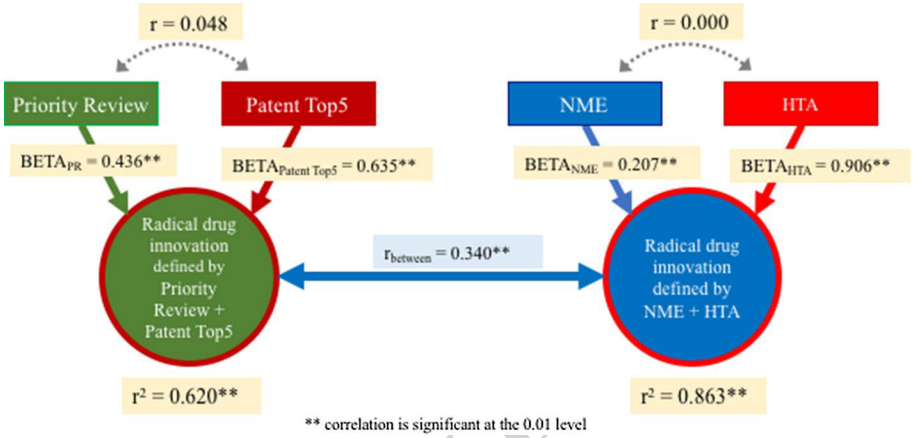

Fig. 6 Convergent validity assessment of the newly developed measure

innovativeness of Mekinist® is assessed using the current measure of novelty plus therapeutic value (*NME* + *Priority Review*), it is classified as an incremental innovation.

For the mandatory benefit assessment of Mekinist® in Germany in 2015, the therapeutic value of the drug was compared against vemurafenib (trade name: Zelboraf®; Gemeinsamer Bundesausschuss 2016b). It was not tested against chemotherapy as it was in the phase 3 METRIC trial, which was the basis of the drug approval by the FDA and the EMA. The benefit assessment resulted in a *considerable additional benefit* rating because the median overall survival increased by 7.6 months for patients treated with Mekinist® when compared with Zelboraf®. Therefore, when applying the newly developed measure that incorporates the HTA approach (*NME* + *HTA*), the drug gets categorized as a radical innovation.

Validating the newly developed measure

Next, we conducted analyses to examine the extent to which the combination of NME and HTA in our newly developed measure form a construct of radical drug innovation. Following Hair et al. (2019) and Hair et al. (2016), the assessment of formative measurement models, as in our case, differs from approaches for reflective measurement models. Formative measurement models are assessed based on indicator collinearity, statistical significance and relevance of the indicator weights, and convergent validity (Hair et al. 2016). As

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such, we assessed our recommended *NME* + *HTA* measure in three steps: Step 1—Evaluate collinearity of the formative indicators; Step 2—Assess the indicator weights' statistical significance and relevance; and Step 3—Assess the convergent validity.

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

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

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

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

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

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

Discussion

Main insights

Radical innovations are vitally important to many industries (Keupp and Gassmann 2013). We focus on the case of radical drug innovations, which are essential for creating competitive advantages for pharmaceutical firms and for dealing with public health issues in the

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

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

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

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

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

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

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

Limitations

As any other, this study is not without limitations. First, innovations were classified into dichotomous categories of radical or incremental innovations, while innovations might be better treated as a continuous variable (Green et al. 1995). However, the fundamental measurement issue addressed in this paper needs to be rectified before fine-tuning the measurement method on a more precise level. Second, the newly developed measure of radical innovation is based on Germany's HTA process. However, the German HTA system, specifically the early benefit assessment that was used for the measurement model, was

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only recently introduced (in 2011) and has been subject to some methodological criticisms (Herpers and Dintsios 2018). For example, HTA examines a new drug's clinical patient-relevant outcome data such as morbidity, mortality, safety, or quality of life (Schlette and Hess 2013). Conflicting opinions exist, though, about the relevant endpoints for different diseases. For instance, the German early benefit assessment considers overall survival as an endpoint for anti-cancer drugs, while Dabisch et al. (2014) argue in favor of progression free survival (i.e., survival time of patients without advancement of their disease) as an endpoint instead. Moreover, critics have raised concerns about how the Federal Joint Committee (G-BA) selects comparator drugs for the early benefit assessments (Leverkus and Chuang-Stein 2016). For example, sometimes the G-BA chooses comparator drugs that are different from those used in clinical development trials for the new drug or they select comparators that differ from those that were used by other HTA bodies in Europe, which disallows comparisons across countries. Moreover, due to the lack of a benefit assessment (primarily because of low sales), 130 drugs had to be excluded from the original data set. This may further narrow the generalizability of the findings to drugs that have moderate to strong sales. Finally, we had to exclude 16 drugs because they had no patents associated with them.

Suggestions for future research

This study highlights the importance of an appropriate measurement model and proposes a potential new measurement method in an effort to further advance the understanding of radical drug innovation and to inspire additional research on the topic. Additional research is needed to more comprehensively assess the utility of the HTA-based measurement model with regard to assessing radical drug innovations. This study suggests a need for additional research using the new measurement model to examine the antecedents and outcomes of radical drug innovations, contrasting findings with previous research that was based on different measurement methods. The current study is an important reminder that the field requires appropriate construct definitions that are in line with current practice and that are directly linked to measurement methods, which need to be validated. Having an appropriate measurement model will provide the foundation to further advance the understanding of radical drug innovation. As Bagozzi et al. (1991, p. 421) remind us: "To bring rigor in research, it is therefore, essential for the researcher to first establish an evidence of construct validity before testing the theory."

References

Achilladelis, B., & Antonakis, N. (2001). The dynamics of technological innovation: The case of the pharmaceutical industry. *Research Policy, 30*(4), 535–588.

Ahuja, G., & Lampert, C. M. (2001). Entrepreneurship in the large corporation: A longitudinal study of how established firms create breakthrough inventions. *Strategic Management Journal, 22*(6–7), 521–543. https://doi.org/10.1002/smj.176

Alqahtani, S., Seoane-Vazquez, E., Rodriguez-Monguio, R., & Eguale, T. (2015). Priority review drugs approved by the FDA and the EMA: Time for international regulatory harmonization of pharmaceuticals? *Pharmacoepidemiology and Drug Safety, 24*(7), 709–715. https://doi.org/10.1002/pds.3793

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Arnold, D. G., & Troyer, J. L. (2016). Does increased spending on pharmaceutical marketing inhibit pioneering innovation? *Journal of Health Politics, Policy and Law, 41*(2), 157.

Aronson, J. K., Ferner, R. E., & Hughes, D. A. (2012). Defining rewardable innovation in drug therapy. *Nature Reviews Drug Discovery, 11*(4), 253–254.

Arundel, A., & Kabla, I. (1998). What percentage of innovations are patented? Empirical estimates for European firms. *Research Policy, 27*(2), 127–141. https://doi.org/10.1016/S0048-7333(98)00033-X

Assink, M. (2006). Inhibitors of disruptive innovation capability: A conceptual model. *European Journal of Innovation Management, 9*(2), 215–233. https://doi.org/10.1108/14601060610663587

Bagozzi, R. P., Yi, Y., & Phillips, L. W. (1991). Assessing construct validity in organizational research. *Administrative Science Quarterly, 36*(3), 421–458. https://doi.org/10.2307/2393203

Bamberger, P. (2017). Construct validity research. *Academy of Management Discoveries, 3*(3), 235–238. https://doi.org/10.5465/amd.2017.0074

Beresniak, A., Auray, J., Duru, G., Medina-Lara, A., Tarricone, R., Sambuc, R., & Lamure, M. (2012). PRM14 European assessment of the validity of the QALY outcome measure: Results from the experiment conducted by the Echoutcome project. *Value in Health, 15*(7), A462.

Beresniak, A., Medina-Lara, A., Auray, J. P., De Wever, A., Praet, J. C., Tarricone, R., & Duru, G. (2015). Validation of the underlying assumptions of the quality-adjusted life-years outcome: Results from the ECHOUTCOME European project. *Pharmacoeconomics, 33*(1), 61–69.

Branch, S. K., & Agranat, I. (2014). "New drug" designations for new therapeutic entities: New active substance, new chemical entity, new biological entity, new molecular entity. *Journal of Medicinal Chemistry, 57*(21), 8729–8765. https://doi.org/10.1021/jm402001w

Brem, A., Maier, M., & Wimschneider, C. (2016). Competitive advantage through innovation: The case of Nespresso. *European Journal of Innovation Management, 19*(1), 133–148. https://doi.org/10.1108/EJIM-05-2014-0055

Cantner, U., Joel, K., & Schmidt, T. (2011). The effects of knowledge management on innovative success – An empirical analysis of German firms. *Research Policy, 40*(10), 1453–1462. https://doi.org/10.1016/j.respol.2011.06.007

Cardinal, L. B., & Hatfield, D. E. (2000). Internal knowledge generation: The research laboratory and innovative productivity in the pharmaceutical industry. *Journal of Engineering and Technology Management, 17*(3–4), 247–271. https://doi.org/10.1016/S0923-4748(00)00025-4

Chambers, J. D., Thorat, T., Wilkinson, C. L., & Neumann, P. J. (2017). Drugs cleared through the FDA's Expedited Review offer greater gains than drugs approved by conventional process. *Health Affairs, 36*(8), 1408–1415. https://doi.org/10.1377/hlthaff.2016.1541

Chandy, R. K., & Tellis, G. J. (1998). Organizing for radical product innovation: The overlooked role of willingness to cannibalize. *Journal of Marketing Research, 35*(4), 474. https://doi.org/10.2307/3152166

Chang, Y.-C., Chang, H.-T., Chi, H.-R., Chen, M.-H., & Deng, L.-L. (2012). How do established firms improve radical innovation performance? The organizational capabilities view. *Technovation, 32*(7–8), 441–451.

Chary, K. V. (2016). Expedited drug review process: Fast, but flawed. *Journal of Pharmacology and Pharmacotherapeutics, 7*(2), 57.

Chiesa, V., Frattini, F., Lamberti, L., & Noci, G. (2009). Exploring management control in radical innovation projects. *European Journal of Innovation Management, 12*(4), 416–443. https://doi.org/10.1108/14601060910996909

Cho, S. Y., & Kim, S. K. (2017). Horizon problem and firm innovation: The influence of CEO career horizon, exploitation and exploration on breakthrough innovations. *Research Policy, 46*(10), 1801–1809. https://doi.org/10.1016/j.respol.2017.08.007

Ciani, O., Armeni, P., Boscolo, P. R., Cavazza, M., Jommi, C., & Tarricone, R. (2016). De innovatione: The concept of innovation for medical technologies and its implications for healthcare policy-making. *Health Policy and Technology, 5*(1), 47–64. https://doi.org/10.1016/j.hlpt.2015.10.005

Cohen, S. K., & Caner, T. (2016). Converting inventions into breakthrough innovations: The role of exploitation and alliance network knowledge heterogeneity. *Journal of Engineering and Technology Management, 40,* 29–44. https://doi.org/10.1016/j.jengtecman.2016.03.002

Cohen, W. M., & Levinthal, D. A. (1990). Absorptive capacity: A new perspective on learning and innovation. *Administrative Science Quarterly, 35*(1), 128–152.

Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. *The New England Journal of Medicine, 372*(9), 793–795. https://doi.org/10.1056/NEJMp1500523

Colombo, M. G., von Krogh, G., Rossi-Lamastra, C., & Stephan, P. E. (2017). Organizing for radical innovation: Exploring novel insights. *Journal of Product Innovation Management, 34*(4), 394–405. https://doi.org/10.1111/jpim.12391

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Cruz-Cázares, C., Bayona-Sáez, C., & García-Marco, T. (2013). You can't manage right what you can't measure well: Technological innovation efficiency. *Research Policy, 42*(6–7), 1239–1250. https://doi.org/10.1016/j.respol.2013.03.012

Dabisch, I., Dethling, J., Dintsios, C.-M., Drechsler, M., Kalanovic, D., Kaskel, P., et al. (2014). Patient relevant endpoints in oncology: Current issues in the context of early benefit assessment in Germany. *Health Economics Review, 4*(1), 2. https://doi.org/10.1186/2191-1991-4-2

Dahlin, K. B., & Behrens, D. M. (2005). When is an invention really radical? *Research Policy, 34*(5), 717–737. https://doi.org/10.1016/j.respol.2005.03.009

Danneels, E., & Kleinschmidt, E. (2001). Product innovativeness from the firm's perspective: Its dimensions and their relation with project selection and performance. *Journal of Product Innovation Management, 18*(6), 357–373.

Darrow, J. J., Avorn, J., & Kesselheim, A. S. (2020). FDA approval and regulation of pharmaceuticals, 1983–2018. *Journal of the American Medical Association, 323*(2), 164–176.

Davis, C., & Abraham, J. (2011). Rethinking innovation accounting in pharmaceutical regulation: A case study in the deconstruction of therapeutic advance and therapeutic breakthrough. *Science, Technology and Human Values, 36*(6), 791–815. https://doi.org/10.1177/0162243910374809

de Solà-Morales, O., Cunningham, D., Flume, M., Overton, P. M., Shalet, N., & Capri, S. (2018). Defining innovation with respect to new medicines: A systematic review from a payer perspective. *International Journal of Technology Assessment in Health Care, 34*(3), 224–240. https://doi.org/10.1017/S0266462318000259

Dewar, R., & Dutton, J. (1986). The adoption of radical and incremental innovations: An empirical analysis. *Management Science, 32*(11), 1422–1433.

Dunlap, D., Marion, T., & Friar, J. (2013). The role of cross-national knowledge on organizational ambidexterity: A case of the global pharmaceutical industry. *Management Learning*. https://doi.org/10.1177/1350507613480099

Dunlap, D., McDonough, E. F., Mudambi, R., & Swift, T. (2016). Making up is hard to do: Knowledge acquisition strategies and the nature of new product innovation. *Journal of Product Innovation Management, 33*(4), 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. *Strategic Entrepreneurship Journal, 4*(2), 106–127. https://doi.org/10.1002/sej.86

Eder, J., Sedrani, R., & Wiesmann, C. (2014). The discovery of first-in-class drugs: Origins and evolution. *Nature Reviews Drug Discovery, 13*(8), 577–587.

European Medicines Agency. (n.d.). *Annual Reports and Work Programmes*. https://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000208.jsp&mid=WC0b01ac058002933a. Last Retrieved on May 7 2018.

European Medicines Agency. (2013). *Stivarga*. https://www.ema.europa.eu/en/medicines/human/EPAR/stivarga. Last Retrieved on September 7 2020.

European Medicines Agency. (2014). *Mekinist*. https://www.ema.europa.eu/en/medicines/human/EPAR/mekinist. Last Retrieved on September 7 2020.

European Patent Office. (n.d.). *PATSTAT*. https://www.epo.org/searching-for-patents/business/patstat.html. Last Retrieved on July 30 2020.

Fagerberg, J., Mowery, D. C., & Nelson, R. R. (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*(2), e0172488.

Fricke, F.-U., & Dauben, H. P. (2009). Health technology assessment: A perspective from Germany. *Value in Health, 12,* S20–S27. https://doi.org/10.1111/j.1524-4733.2009.00555.x

Garcia, R., & Calantone, R. (2002). A critical look at technological innovation typology and innovativeness terminology: A literature review. *Journal of Product Innovation Management, 19*(2), 110–132.

Gemeinsamer Bundesausschuss. (n.d.). *The benefit assessment of medicinal products in accordance with the german social code, book five (Sgb V), Section 35a*. https://www.g-ba.de/english/benefitassessment. Last Retrieved on September 9 2020.

Gemeinsamer Bundesausschuss. (2016a, March). *Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Regorafenib*. https://www.g-ba.de/downloads/40-268-3667/2016-03-17_AM-RL-XII_Regorafenib_2015-10-01-D-189_TrG.pdf. Last Retrieved on September 7 2020.

Gemeinsamer Bundesausschuss. (2016b). *Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Trametinib*. https://www.g-ba.de/downloads/40-268-3668/2016-03-17_AM-RL-XII_Trametinib_2015-10-01-D-183_TrG.pdf. Last Retrieved on September 7 2020.

Gopalakrishnan, S., & Damanpour, F. (1997). A review of innovation research in economics, sociology and technology management. *Omega, 25*(1), 15–28.

Green, S. G., Gavin, M. B., & Aiman-Smith, L. (1995). Assessing a multidimensional measure of radical technological innovation. *IEEE Transactions on Engineering Management, 42*(3), 203–214. https://doi.org/10.1109/17.403738

Hagedoorn, J., & Cloodt, M. (2003). Measuring innovative performance: Is there an advantage in using multiple indicators? *Research Policy, 32*(8), 1365–1379.

Hair, J. F., Risher, J. J., Sarstedt, M., & Ringle, C. M. (2019). When to use and how to report the results of PLS-SEM. *European Business Review, 31*(1), 2–24.

Hair, J. F., Jr., Hult, G. T. M., Ringle, C., & Sarstedt, M. (2016). *A primer on partial least squares structural equation modeling (PLS-SEM)*. London: Sage Publications.

Hernandez-Espallardo, M., Molina-Castillo, F., & Rodriguez-Orejuela, A. (2012). Learning processes, their impact on innovation performance and the moderating role of radicalness. *European Journal of Innovation Management, 15*(1), 77–98. https://doi.org/10.1108/14601061211192843

Herpers, M., & Dintsios, C.-M. (2018). Methodological problems in the method used by IQWiG within early benefit assessment of new pharmaceuticals in Germany. *The European Journal of Health Economics, 2*(1), 45–57.

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. *Research Policy, 45*(3), 682–698.

Hwang, T. J., Franklin, J. M., Chen, C. T., Lauffenburger, J. C., Gyawali, B., Kesselheim, A. S., & Darrow, J. J. (2018). Efficacy, safety, and regulatory approval of food and drug Administration-designated breakthrough and nonbreakthrough cancer medicines. *Journal of Clinical Oncology, 36*(18), 1805–1812.

Jayadev, A., & Stiglitz, J. (2009). Two ideas to increase innovation and reduce pharmaceutical costs and prices. *Health Affairs, 28*(1), 165–168. https://doi.org/10.1377/hlthaff.28.1.w165

Jiménez-Jimenez, D., Sanz Valle, R., & Hernandez-Espallardo, M. (2008). Fostering innovation: The role of market orientation and organizational learning. *European Journal of Innovation Management, 11*(3), 389–412. https://doi.org/10.1108/14601060810889026

Johannessen, J., Olsen, B., & Lumpkin, G. T. (2001). Innovation as newness: What is new, how new, and new to whom? *European Journal of Innovation Management, 4*(1), 20–31. https://doi.org/10.1108/14601060110365547

Kanter, R. (1983). *The change masters*. New York: Simon and Schuster.

Kaplan, S., & Vakili, K. (2015). The double-edged sword of recombination in breakthrough innovation. *Strategic Management Journal, 36*(10), 1437–1457.

Kennedy, I. (2009). Appraising the value of innovation and other benefits: A short study for London: NICE.

Kesselheim, A. S., Wang, B., & Avorn, J. (2013). Defining "innovativeness" in drug development: A systematic review. *Clinical Pharmacology and Therapeutics, 94*(3), 336–348. https://doi.org/10.1038/clpt.2013.115

Keupp, M. M., & Gassmann, O. (2013). Resource constraints as triggers of radical innovation: Longitudinal evidence from the manufacturing sector. *Research Policy, 42*(8), 1457–1468. https://doi.org/10.1016/j.respol.2013.04.006

Kneller, R. (2010). The importance of new companies for drug discovery: Origins of a decade of new drugs. *Nature Reviews Drug Discovery, 9*(11), 867–882. https://doi.org/10.1038/nrd3251

Kuhn, J., Younge, K., & Marco, A. (2020). Patent citations reexamined. *The RAND Journal of Economics, 51*(1), 109–132.

Lauenroth, V. D., & Stargardt, T. (2017). Pharmaceutical pricing in Germany: How is value determined within the scope of AMNOG? *Value in Health, 20*(7), 927–935. https://doi.org/10.1016/j.jval.2017.04.006

Lazzeri, F., Pisano, G. P. (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.

Leverkus, F., & Chuang-Stein, C. (2016). Implementation of AMNOG: An industry perspective. *Biometrical Journal, 58*(1), 76–88. https://doi.org/10.1002/bimj.201300256

Lexchin, J. (2016). How safe and innovative are first-in-class drugs approved by health Canada: A cohort study. *Healthcare Policy, 12*(2), 65.

Malva, A. D., Kelchtermans, S., Leten, B., & Veugelers, R. (2015). Basic science as a prescription for breakthrough inventions in the pharmaceutical industry. *Journal of Technology Transfer, 40*(4), 670–695. https://doi.org/10.1007/s10961-014-9362-y

McDermott, C. M., & O'Connor, G. C. (2002). Managing radical innovation: An overview of emergent strategy issues. *Journal of Product Innovation Management, 19*(6), 424–438.

Midgley, D. F., & Dowling, G. R. (1978). Innovativeness: The concept and its measurement. *Journal of Consumer Research, 4*(4), 229–242.

Morgan, S., Lopert, R., & Greyson, D. (2008). Toward a definition of pharmaceutical innovation. *Open Medicine, 2*(1), e4.

Mostaghim, S. R., Gagne, J. J., & Kesselheim, A. S. (2017). Safety related label changes for new drugs after approval in the US through expedited regulatory pathways: Retrospective cohort study. *British Medical Journal, 358,* j3837.

Noblet, J.-P., Simon, E., & Parent, R. (2011). Absorptive capacity: A proposed operationalization. *Knowledge Management Research and Practice, 9*(4), 367–377. https://doi.org/10.1057/kmrp.2011.26

OECD (2015). *New Sources of Growth: Phase 2, Knowledge-based Capital. Enquiries into Intellectual Property's Economic Impact.* Retrieved August 23 2020 from https://www.oecd.org/sti/ieconomy/intellectual-property-economic-impact.htm.

Olson, M. K. (2008). The risk we bear: the effects of review speed and industry user fees on new drug safety. *Journal of Health Economics, 27*(2), 175–200.

Orianaa, C., Patrizioa, A., Robertaa, B. P., Mariannaa, C., Claudioa, J., & Rosanna, T. (2016). *De innovatione*: The concept of innovation for medical technologies and its implications for healthcare policy-making. *Health Policy and Technology, 5*(1), 47–64.

Ouellette, L. L. (2010). How many patents does it take to make a drug? Follow-on pharmaceutical patents and university licensing. *Michigan Telecommunications and Technology Law Review, 17*(299), 2010–2011.

Panteli, D., Eckhardt, H., Nolting, A., Busse, R., & Kulig, M. (2015). From market access to patient access: Overview of evidence-based approaches for the reimbursement and pricing of pharmaceuticals in 36 European countries. *Health Research Policy and Systems.* https://doi.org/10.1186/s12961-015-0028-5

Phene, A., Fladmoe-Lindquist, K., & Marsh, L. (2006). Breakthrough innovations in the US biotechnology industry: The effects of technological space and geographic origin. *Strategic Management Journal, 27*(4), 369–388.

Pinnow, E., Amr, S., Bentzen, S. M., Brajovic, S., Hungerford, L., & George DalPan, D. M. G. (2018). Postmarket safety outcomes for new molecular entity (NME) drugs approved by the Food and Drug Administration between 2002 and 2014. *Clinical Pharmacology and Therapeutics, 104*(2), 390–400.

Postma, M. J., Boersma, C., Vandijck, D., Vegter, S., Le, H. H., & Annemans, L. (2011). Health technology assessments in personalized medicine: Illustrations for cost–effectiveness analysis. *Expert Review of Pharmacoeconomics and Outcomes Research, 11*(4), 367–369. https://doi.org/10.1586/erp.11.50

Salavou, H. (2004). The concept of innovativeness: Should we need to focus? *European Journal of Innovation Management, 7*(1), 33–44. https://doi.org/10.1108/14601060410515628

Scheithauer, W. (2012). Faculty opinions recommendation of Grothey A et al. Lancet. *Faculty Opinions.* https://doi.org/10.3410/f.717965145.793466450

Schlette, S., & Hess, R. (2013). Issues in international health policy. *Issue brief (Commonwealth Fund), 29,* 1–9.

Schmid, E. F., & Smith, D. A. (2005). Managing innovation in the pharmaceutical industry. *Journal of Commercial Biotechnology, 12*(1), 50–57.

Shane, S. (2001). Technological opportunities and new firm creation. *Management Science, 47*(2), 205–220.

Singh, J., & Fleming, L. (2010). Lone inventors as sources of breakthroughs: Myth or reality? *Management Science, 56*(1), 41–56. https://doi.org/10.1287/mnsc.1090.1072

Skipka, G., Wieseler, B., Kaiser, T., Thomas, S., Bender, R., Windeler, J., et al. (2016). Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs: Determine minor, considerable and major treatment effects. *Biometrical Journal, 58*(1), 43–58. https://doi.org/10.1002/bimj.201300274

Smith, K. J., & Roberts, M. S. (2000). The cost–effectiveness of sildenafil. *Annals of Internal Medicine, 132,* 933–937.

Sorescu, A. B., Chandy, R. K., & Prabhu, J. C. (2003). Sources and financial consequences of radical innovation: Insights from pharmaceuticals. *Journal of Marketing, 67*(4), 82–102.

Stafford, R. S., Wagner, T. H., & Lavori, P. W. (2009). New, but not improved? Incorporating comparative-effectiveness information into FDA labeling. *New England Journal of Medicine, 361*(13), 1230–1233. https://doi.org/10.1056/NEJMp0906490

Sternitzke, C. (2010). Knowledge sources, patent protection, and commercialization of pharmaceutical innovations. *Research Policy, 39*(6), 810–821.

Suzuki, O., & Methe, D. T. (2014). Local search, exploration frequency, and exploration valuableness: Evidence from new pharmaceuticals development. *International Journal of Innovation Management, 18*(02), 1450014. https://doi.org/10.1142/S1363919614500145

thinkBiotech LLC. (n.d.). *Drug patent watch*. https://www.drugpatentwatch.com. Last Retrieved on July 7 2020.

Tijssen, R. J. W. (2001). Global and domestic utilization of industrial relevant science: Patent citation analysis of science-technology interactions and knowledge flows. *Research Policy, 30*(1), 35–54. https://doi.org/10.1016/S0048-7333(99)00080-3

Trajtenberg, M. (1990). A penny for your quotes: Patent citations and the value of innovations. *The Rand Journal of Economics, 21,* 172–187.

Trajtenberg, M., Henderson, R., & Jaffe, A. (1997). University versus corporate patents: A window on the basicness of invention. *Economics of Innovation and New Technology, 5*(1), 19–50.

Tushman, M. L., & Anderson, P. (1986). Technological discontinuities and organizational environments. *Administrative Science Quarterly, 31*(3), 439. https://doi.org/10.2307/2392832

US Food & Drug Administration. (n.d.-a). *Orange Book: Approved drug products with therapeutic equivalence evaluations*. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Last Retrieved on August 20 2020.

US Food & Drug Administration. (n.d.-b). *Purple book database of licensed biological products*. https://purplebooksearch.fda.gov. Last Retrieved on August 20 2020.

US Food & Drug Administration. (n.d.-c). *Drugs@FDA: FDA-Approved Drugs*. https://www.fda.gov/drugsatfda. Last Retrieved on May 7 2018.

US Food & Drug Administration. (2012, September 20). *Center for Drug Evaluation and Research Application Number 203085Orig1s000 Summary Review*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203085Orig1s000SumR.pdf. Last Retrieved on September 7 2020.

US Food & Drug Administration. (2013, May 28). *Center for Drug Evaluation and Research Application Number 204114Orig1s000 Summary Review*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204114Orig1s000SumR.pdf. Last Retrieved on September 7 2020.

US Food & Drug Administration. (2018, February 23). *Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review*. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review. Last Retrieved on September 5 2020.

US Food & Drug Administration. (2020). *Advancing health through innovation: New drug therapy approvals 2019.* https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2019. Last Retrieved on August 20 2020.

US National Library of Medicine. (2015, June 24). *Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy*. https://clinicaltrials.gov/ct2/show/NCT01103323. Last Retrieved on September 7 2020.

US National Library of Medicine. (2018, April 5). *GSK1120212 vs Chemotherapy in advanced or metastatic BRAF V600E/K Mutation-positive Melanoma*. https://clinicaltrials.gov/ct2/show/NCT01245062. Last Retrieved on September 7 2020.

Verhoeven, D., Bakker, J., & Veugelers, R. (2016). Measuring technological novelty with patent-based indicators. *Research Policy, 45*(3), 707–723. https://doi.org/10.1016/j.respol.2015.11.010

Wallach, J. D., Ross, J. S., & Naci, H. (2018). The US Food and Drug Administration's expedited approval programs: Evidentiary standards, regulatory trade-offs, and potential improvements. *Clinical Trials, 15*(3), 219–229.

Wang, C. L., & Ahmed, P. K. (2004). The development and validation of the organisational innovativeness construct using confirmatory factor analysis. *European Journal of Innovation Management, 7*(4), 303–313.

Weinstein, M. C., Russell, L. B., Gold, M. R., & Siegel, J. E. (1996). *Cost-effectiveness in health and medicine*. New York: Oxford University Press.

Wieseler, B., McGauran, N., & Kaiser, T. (2019). New drugs: Where did we go wrong and what can we do better? *British Medical Journal, 366,* l4340.

Yamin, M., & Otto, J. (2004). Patterns of knowledge flows and MNE innovative performance. *Journal of International Management, 10*(2), 239–258. https://doi.org/10.1016/j.intman.2004.02.001

Zucker, L. G., Darby, M. R., & Armstrong, J. S. (2002). Commercializing knowledge: University science, knowledge capture, and firm performance in biotechnology. *Management Science, 48*(1), 138–153. https://doi.org/10.1287/mnsc.48.1.138.14274