The Decline of Innovation in the Antibiotics Industry and the Global Threat of Antibiotic Resistance: When Entrepreneurial Efforts are Not Enough

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Abstract In this chapter we intend to analyze the worrisome case of the antibiotics industry, as the number of active firms, innovation output and profitability has constantly declined in the last years. With a focus on factors influencing the Entrepreneurial Orientation of firms in this industry, we analyze a number of challenges and environmental contingencies unique to antibiotic innovation and entrepreneurial activity, and discuss currently debated public policy interventions intended to reinvigorate the industry. In doing so we discuss the possibility of enhancing entrepreneurial orientation by acting on the performance side through targeted public interventions such as research grants and market entry rewards. This chapter contributes to innovation and entrepreneurship literature by presenting a unique case of a declining industry, the antibiotics field, which requires public intervention to revive and meet global societal needs to face the threat of antibiotic resistance. This industry-based case analysis presents a number of interesting implications for theory on Entrepreneurial Orientation that also allows the outlining of several avenues for future research.

Keywords Innovation · Entrepreneurial orientation · Public intervention · Antibiotics industry

1 Introduction

The antibiotic industry is in decline at the same time as society worldwide desperately needs new antibiotics to face the global threat of antibiotic resistance. In the past 20 years, an increasing number of companies have exited the antibiotics market and the number of new entrants is very limited. These circumstances have today resulted in a lack of innovation with only few big pharmas still active in the field, and

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a global antibiotics pipeline with extremely limited numbers of promising new molecules.

Although there still are small, entrepreneurial companies trying to develop novel antibiotics, without big pharmas to purchase their molecules there is little hope for continued innovation and improved industry dynamics. How to stimulate innovation and entrepreneurial activity in an industry in decline? In this chapter we intend to analyze the current status of the antibiotics sector with a focus on factors influencing the Entrepreneurial Orientation of firms in this industry. More specifically, we start by presenting the current status of the antibiotics industry and also by analyzing a number of challenges unique to innovation and entrepreneurial activity in this industry. We present such entrepreneurial and innovation-related challenges according to their scientific, financial, or market-specific nature. Consequently, we will also discuss potential public policy interventions to stimulate new entrepreneurial activities and related antibiotic innovation in this industry. In particular, the most important public interventions are discussed in terms of their potential effects (both benefits and risks) on future innovation and entrepreneurial activities given the previously identified challenges of the antibiotic field. Analyzing the effect of intervention mechanisms on the Entrepreneurial Orientation of firms in this industry will be given particular attention. The decline of an entire industry has been found to manifest itself through the lack of entrepreneurial orientation and firm performance (Lumpkin and Dess 2001). In this study, we attempt to explain the lack of firm performance, and by implication also long-term entrepreneurial orientation, by analyzing a number of environmental contingencies which may be suffocating the antibiotics industry.

This chapter contributes to innovation and entrepreneurship literature by presenting a unique case of a declining industry, the antibiotics field, which requires public intervention to revive and meet global societal needs to face the threat of antibiotic resistance. Analyzing this specific industry case also has a number of interesting implications for theory on Entrepreneurial Orientation that allows the outlining of several avenues for future research.

The remainder of this chapter is structured as follows: after introducing the current status of the antibiotic industry we move on to depict the current main (scientific, financial and market-related) challenges that firms face in this industry. In the part that follows we make use of the Entrepreneurial Orientation framework to analyze these challenges as well as currently discussed public interventions to stimulate investments and entrepreneurial activities in the antibiotic industry. This analysis paves the way for our concluding discussion that puts in relation targeted public interventions, environmental contingencies and firms' performance with the level of Entrepreneurial Orientation in the industry. At last we will present some suggestions for future research.

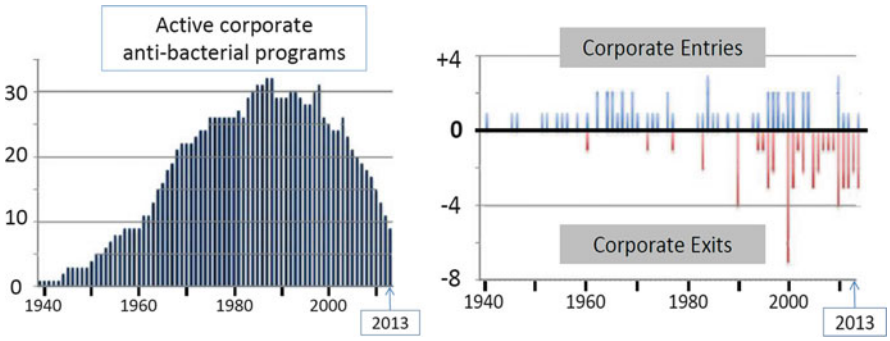

Fig. 1 The withdrawal of firms from the antibiotics industry. Source: Adapted from Kinch et al., Drug Discovery Today (2014)

2 The Current Status of the Antibiotics Industry

The antibiotic industry suffers from a lack of innovation and investment from the main actors in the industry, as well as a dearth of new entrants (Fig. 1). As a consequence, the industry is in a long and steep decline as pharmaceutical companies are increasingly closing down their antibiotic research and development (R&D) labs (Rex and Outterson 2016). For comparison, there were 25 large pharmaceutical firms with ongoing antibacterial drug discovery programs in 1980; in 2014 only four remained (Boucher et al. 2009) two of which had an antibacterial in phase two of development. Sadly, out of these four active programs, an additional two have been closed since 2014 (AstraZeneca and Cubist).

This decline in active antibacterial drug discovery programs has taken place in the face of rising threats from multi-drug resistant bacteria. Antibiotic resistance, i.e., when bacteria become resistant to existing antibiotics, is a growing global threat to public health and makes the decline of the antibiotics industry uniquely problematic. While considerable advances have been made in the areas of vaccines, sanitation, and infection control, antibiotics remains a pillar of infectious disease therapy. Often referred to as the backbone of modern medicine, antibiotics are used to save lives by killing dangerous bacteria in everything from pneumonia and urinary tract infections to treatments like surgery and chemotherapy.

While hard to calculate with precision, the consequences of antibiotic resistance are huge in both human health and economic cost. Since penicillin first became widely used in the 1940s, the fear has been that bacteria in time would mutate and find ways to defend themselves against the miracle drug of antibiotics. Indeed, the increasing prevalence of antibiotic resistance is eroding the efficacy of existing antibiotics (Laxminarayan et al. 2014). These antibiotic-resistant bacteria have become increasingly common and today are confirmed to kill 100,000 people per year in the US, the EU and Thailand—the only countries from which data is currently available. However, the global numbers believed to die from antibiotic-resistant

bacteria are thought to be in the several hundreds of thousands (O'Neill Commission 2015).

Taken together, these developments have presented a pressing need to reverse the decline of the antibiotics industry and to restore the industry's innovation pipeline to good health. However, reversing this decline requires first identifying the main challenges to innovation in antibiotics, which, as we will discuss in the next section, are numerous.

In order to outline the situation facing the antibiotics industry, we will first present the main challenges to antibiotic innovation from a business perspective followed by examples of the main responses to the crisis of the antibiotics industry that lately have been discussed on supra-national levels, such as at the G20 and the UN. Finally, we will present a framework through which we believe that the challenges facing the antibiotics industry may be understood as a whole and the feasibility of the solutions to these problems may be evaluated—the framework of Entrepreneurial Orientation. Having analyzed the antibiotic industry through this lens, we provide important implications for firms, policy makers, and theory on entrepreneurship and innovation.

3 Challenges Facing the Antibiotics Industry

There are a number of factors conspiring to cause lack of entrepreneurial activities in the antibiotic industry.[1] The most pressing challenges are related to innovation and profitability.

From a scientific standpoint, what can be referred to as the "low-hanging fruit" has been picked and novel discoveries are increasingly both costly and scarce. Moreover, there are a number of factors related to pharmaceutical innovation regulations and so-called stewardship—the responsible (restrictive) use of new antibiotics—that increase the scientific and business challenges to antibiotics R&D.

Developers who come up with new antibiotics create considerable benefit for society but are not guaranteed to benefit financially (O'Neill Commission 2015). Industry consolidation has resulted in a major decrease in the hunt for novel

[1] *Methodological note:* The analysis of the antibiotics industry in this chapter is based on data collected within a larger research project in which multiple data collection methods were applied. A separate literature review of challenges facing innovation in the antibiotic industry was conducted. A focus group of experts from both academia, public health, and the pharmaceutical industry reviewed the final list of challenges. When initially analyzing the collected data we focused on facts and specific statements rather than on opinions (Eisenhardt 1989; Eisenhardt and Graebner 2007) and in our initial analysis of these challenges we did no additional interpretation of beyond that already present in the data. Our data collection efforts resulted in an exhaustive document outlining the known challenges to innovation in antibiotics. However, for the purpose of the analysis performed in this book chapter, only a subset of such challenges was used. These challenges were those most closely pertaining to the business of antibiotics, i.e., to sales market growth, competition, and innovation. These challenges are presented in the coming section in their original format to facilitate the later analysis using the entrepreneurial orientation framework.

antibiotic agents (Projan and Shlaes 2004). This, in turn, is thought to be caused by a lack of commercial attractiveness to off-set the costs and risks involved in the development of antibiotics. Most antibiotics generate annual revenues of US$ 200–300 million, while the costs of bringing any drug to market have been estimated to be as high as US$ 400–800 million (DiMasi et al. 2003). Moreover, the financial risk associated with involvement in antibiotics R&D acts as a disincentive (Pray 2008). High costs and high risk together have the effect that important investment metrics such as Net Present Values (NPVs) and Return On Investments (ROIs) for antibiotics are either negative (Spellberg et al. 2015) or lower than for other pharmaceutical treatments, making antibiotics an unattractive therapeutic investment (Payne et al. 2015; Power 2006; Projan 2003; Wright 2015). As a consequence, antibiotics get lower priority than other drugs (Projan and Shlaes 2004), as current R&D trends emphasize chronic diseases (Spellberg et al. 2004). However, these financial challenges to antibiotic innovation and entrepreneurship can be seen to have deeper root causes, which is the topic to which we turn next. Below, we present more in detail a set of challenges pertaining to the financial, market and scientific areas of the global antibiotic industry.

3.1 Pricing

Antibiotics are typically priced much lower than other drugs (Spellberg et al. 2015) and limitations on the pricing of new antibiotics persist (Harbarth et al. 2015). Moreover, reimbursement systems encourage the use of the cheapest drug (Morel and Mossialos 2010; Renwick et al. 2014) and healthcare payers are neither accustomed nor prepared to reimburse antibiotics at higher prices, which would provide incentives to start or maintain antibacterial drug development programs (Laxminarayan and Powers 2011). Additionally, tightening restrictions for placement on hospital formularies negatively affects antibiotics R&D (Harbarth et al. 2015) and increased regulatory measures negatively impact potential revenues by increasing development costs, limiting the number of indications or diseases for which a drug can be recommended as standard treatment (Power 2006). Lastly, flaunting of intellectual property laws has resulted in the proliferation of low priced generics, which created a distortion of the market for anti-infective drugs (Projan 2003). All the above listed factors point to the fact that improving revenue streams and profit margins in this industry is very difficult to accomplish.

3.2 Revenues and Market Sizes

There is tremendous uncertainty associated with the peculiar dynamics of the antibiotics marketplace (O'Neill Commission 2015). For example, it has been highlighted how hard it is for pharmaceutical firms to predict how big the health

need will be in the future as they try to make decisions about very long-term investments in R&D (O'Neill Commission 2015; Zorzet 2014). This, in turn, is made particularly difficult in the antibiotics industry due to the uncertainties surrounding resistance development and as the rate of infections can change quickly (O'Neill Commission 2015).

The revenues attained from a novel antibiotic have been found to be negatively affected by the generally short courses of treatment (Renwick et al. 2014). Specifically, this affects NPV (Morel and Mossialos 2010; Spellberg et al. 2015) or ROI (Katz et al. 2006; NIAID 2014) by reducing the potential "peak" revenue attainted even if a novel antibiotic gains a large market share (Payne et al. 2015). Lastly, the potential of accruing revenues from novel antibiotics are also depressed as resistance may itself limit an antibiotic's lifespan (So et al. 2011).

Adding to the challenges of difficult-to-predict future markets and low peak-year sales, there is moreover a high level of competition for newly developed antibiotics (Payne et al. 2007; So et al. 2011; Spellberg et al. 2004). In addition, new drugs will probably only become prioritized treatments many years after introduction (O'Neill Commission 2015), pushing the prospects of much needed revenues further into the future. As a consequence of these challenges, recently launched antibiotics developed to target resistance have not captured as much of the market share as anticipated (Payne et al. 2015; Projan 2003), essentially dis-incentivizing the development of new antibiotics (Outterson et al. 2007).

Part of the reason why new antibiotics become the treatment-of-choice only after many years is that the medical community discourages the use of newly developed antibiotics to preserve their efficacy in case of rapid future increases in antibiotic resistance (Spellberg et al. 2004).

Research has estimated that the worldwide sales revenue (in 2000 US$) over the product life cycle for a new antibiotic approved in the US during 1990–1994 to be on average US$2379 million. This compares to an average of US$4177 million for central nervous system drugs and US$3668 million for cardiovascular drugs (DiMasi et al. 2004). But not only did antibiotics bring in less revenues than other drugs, they also showed an average annual growth of 4% over the past 5 years, compared with a growth of 16.7% and of 16.4% for antiviral drugs and vaccines, respectively (Hamad 2010).

Taken together, the challenges presented above point to the fact that attaining revenues and market share is particularly tough in the antibiotics industry.

3.3 Portfolio and Competition

One 'industry effect' that poses a challenge to antibiotics R&D is, in the case of larger pharmaceutical companies, that various competing projects must be prioritized relative to each other (Projan 2003). Low NPV or ROI for antibiotics incentivizes companies to shift their investments towards chronic illnesses in for example the oncology or cardiovascular therapeutic areas (Finch and Hunter 2006; Katz et al. 2006; Morel and

Mossialos 2010; Power 2006; Projan 2003; Spellberg et al. 2015), since better returns can be made in other areas than antibiotics (Payne et al. 2007).

The antibiotics industry is increasingly faced with a large number of inexpensive off-patent antibiotics (Harbarth et al. 2015; Renwick et al. 2014) and pharmaceutical companies have difficulty competing against such generic manufacturers (Projan 2003), since the latter do not bear the costs and risks of drug development (Power 2006). This competition from generic producers has in turn had a negative effect on the willingness of research-focused pharmaceutical firms to invest in antibiotics R&D (Projan and Shlaes 2004).

Funding is the lifeblood of early-stage activities in the antibiotics field. In general, small pharmaceutical firms rely on large companies to provide the funding for the expensive phase III clinical trial studies (Projan and Shlaes 2004). Yet since antibiotics traditionally fail early and often, the appetite of the venture capital market to fund small companies during discovery and early development phases of research has been much reduced (Friedman and Alper 2014). Unfortunately, this lack of funding causes many potentially valuable projects to fail to get off the ground (O'Neill Commission 2015).

All the above listed challenges suggest that antibiotics suffer from competition not only against cheap generic manufacturers and off-patent antibiotics, but also internally in large pharmaceutical firms for funding against other therapeutic areas, and in the case of small pharmaceutical firms for fundraising from VCs in competition with other pharmaceutics/biotech businesses.

3.4 Costs of Resistance and Stewardship

Antibiotics R&D is negatively affected by the fact that antibiotics are becoming progressively ineffective due to antibiotic resistance (Renwick et al. 2014), thus shortening the clinical lifespan of antibiotics (Katz et al. 2006; Morel and Mossialos 2010; Payne et al. 2015; Power 2006) and as a consequence also negatively influences the ability of sales to recoup the costs of innovation (Power 2006). Moreover, national conservation programs and other kinds of antibiotic stewardship negatively affects sales (Renwick et al. 2014; Spellberg et al. 2015) and so does public health measures that aim to limit antibiotics use (Power 2006; Rubin 2004; Spellberg 2008). Lastly, active efforts to conserve antibiotics through rational use guidelines curb the opportunity to expand markets (So et al. 2011).

As we can see, both attempts to fight antibiotic resistance (stewardship) and resistance itself are undermining the development of novel antibiotics by reducing as well as creating uncertainty around the prospects of future sales.

3.5 R&D Challenges

In recent years there has been little success in developing novel antibiotics (Payne et al. 2015). As examples of this lack of progress, only 7% (at GlaxoSmithKline) or 6.5% (at Pfizer) of search efforts directed at finding new antibiotics have been successful, while other therapeutic areas have seen approximately ten times greater success (Projan 2003).

Attempts to use new, automated, techniques to find potential new antibiotics have resulted in closures of corporate labs that used to pursue traditional, exploratory research into antibiotics. As a consequence, pharmaceutical companies now have a dwindling capacity with regards to effective antibiotics development (Laxminarayan et al. 2014). Moreover, the pharmaceutical industry has down-sized interdisciplinary innovation environments in which risk-accepting, long-term experimentation was favored, and has therefore been argued to a considerable extent have lost its capacity to discover new antibiotics (ReAct 2011). As many pharmaceutical companies have reallocated scientific talent and capacity to more profitable opportunities, they have also diminished the economies of scale they originally possessed (Renwick et al. 2014).

As the new ways of searching for potentially novel antibiotics did not produce results, firms were lead to develop drugs that were variations of old ones, rather than novel therapies (Poupard 2006). Complex regulatory requirements relating to pre-clinical data and a tendency towards misinterpretation of toxicity data (whether an antibiotic is toxic not only to the target bacteria, but also to the patient) has been identified to pose obstacles to antibiotics R&D (Bridging the Gap 2012; Friedman and Alper 2014).

Some of the scientific difficulties are due to the fact that bacteria have multiple means of defending itself from drugs, above and beyond resistance (Payne et al. 2007). These multiple means of defending against drugs seem to be at work simultaneously and have been argued not to have been given enough attention in clinical research (Stewart and Costerton 2001; ReAct 2011). Additionally, the issue of resistance potential has not been given enough attention and has likely not been assessed correctly in drug development of antibiotics (ReAct 2011).

The challenges presented above contribute to that antibiotic R&D has a higher failure rate than other therapeutics (Payne et al. 2015), that is faces increasing costs for clinical trials (Bridging the Gap 2012; Katz et al. 2006; Payne et al. 2015; Zorzet 2014) as well as increasing development time (Katz et al. 2006; Payne et al. 2015; Spellberg et al. 2004). This suggests that there are important intrinsic R&D-related challenges critically influencing the antibiotics field.

4 Public Awareness and Policy Interventions

Taken together, the many challenges facing innovation in antibiotics has had the effect of essentially suffocating this critically important industry. Although it has been long in the making, the more recent and rapid rise in antibiotic resistance has put the problems of the antibiotics industry on the agenda of policy makers, academics, and health professionals alike. There is now a common understanding that this industry must be revived if we are to avoid a post-antibiotic era where medical progress in important areas takes a 70-year step backwards.

On the policy-making level, politicians in the most advanced countries are currently discussing the emergency of the antibiotic resistance problem. For the fourth time in its history the UN has brought a health-related problem to the official agenda: the threat of antibiotic resistance.

On the industry-side, the G20 meeting in July 2017 dealt with decisions on how to best tackle this global threat as a top priority on their agenda. Media are repeatedly and increasingly taking up the antibiotic resistance issue to raise public awareness. Billions in funding from many different countries is going to be spent on tackling the problem. How to best invest these resources is crucial. The role of firms is an important, yet missing, piece of this puzzle. A *"Declaration on Combating Antimicrobial Resistance"* was drafted and signed by 85 companies and 9 industry associations across 18 countries at the 2016 World Economic Forum in Davos, Switzerland, showing their intent to take part in confronting antibiotic resistance before we find ourselves in a catastrophic post-antibiotic era.

However, on a more practical note and as a consequence of the growing insight into the need for public intervention in order to revive the antibiotics industry, a number of different kinds of such interventions are currently being planned. Two much discussed interventions discussed by policy makers in both the EU and the US are the push intervention "Targeted Grants", and the pull intervention "Market Entry Rewards". These are two quite simple and straight-forward ideas which will be presented in their essence below. However, the effects that these two different interventions may have on the antibiotic industry are much less obvious, as will be discussed at length later in the analysis.

4.1 Targeted Grants (Push)

Targeted Grants is a public intervention that serves the purpose of directly reducing firms' R&D costs for developing new antibiotics which are deemed necessary and urgent for society. This is done by providing funds to firms that are currently developing critically needed antibiotics as they are in the process of developing them. The purpose of a targeted grant is thereby to provide free funding that may "tip the scales" of a firm's investment calculation and thereby allow the development of a particular, targeted antibiotic to move forward.

4.2 Market Entry Reward (Pull)

The type of public intervention called a Market Entry Reward (MER) is a large sum of money given to any firm that brings an antibiotic with a certain ex-ante specified profile to market. Such profile is supposed to reflect the most urgent unmet clinical need, i.e., the antibiotic should target multi-drug resistant bacteria that at present is hard to kill or perhaps only can be killed with one kind of antibiotic (which might seize working in the future). The MER, then, is essentially a sum of money that is large enough to compensate the developer of the new and needed antibiotic for the risks and costs incurred.

A MER is intended to have the effect of increasing the revenue from an antibiotic at the time it is brought to market. Paying a MER provides a firm with a large revenue that offsets costs of R&D more powerfully than sales in the market would, as sales would occur over many years and thus be worth less due to the "time-value of money" where revenues in the future are worth less than the same amounts would be today.

One of the main benefits of a MER is that is can be so-called "fully delinked". This means that the MER will be awarded as a substitute, not a complement, to market sales, thereby not allowing for the antibiotic in question to be freely sold on the market. This is an attractive feature since it prevents over-consumption that may lead to resistance.

5 Entrepreneurial Orientation

To help understand the problems facing the antibiotics industry and the attempts to alleviate these problems and revive the industry through public interventions, we will make use of an analytical framework based in the literature on entrepreneurial orientation.

Research in entrepreneurship has repeatedly found that firms vary in their degree of entrepreneurial orientation and that this variation is related to differences in firm performance (Covin and Miller 2014; Lumpkin and Dess 1996; Rauch et al. 2009; Saeed et al. 2014). The particular framework of entrepreneurial orientation that we will base our analysis on, originally presented by Lumpkin and Dess (1996), was designed to explain the entrepreneurial behavior of firms in an industry and the relation between this behavior and firm performance. Lumpkin and Dess (1996) specifically contributed by summarizing literature on the topic and emphasizing what they refer to as "contingencies" on the main relationship between entrepreneurial orientation and firm performance as will be explained below. In this chapter, we will use this framework as an analytical lens through which we will attempt to explain not the link between entrepreneurial orientation and firm performance of the single firm, but rather the general decline of all firms of the antibiotics industry. A prominent reason why research on entrepreneurial orientation is suitable for

analyzing the challenges facing the antibiotics industry is that an entrepreneurial orientation has been found to help firms that are facing risk and uncertainty in their industry to act entrepreneurially in seizing and exploiting business opportunities in that industry (Covin and Slevin 1991; Lumpkin and Dess 1996; Rosenbusch et al. 2013; Wiklund and Shepherd 2003). Although the entrepreneurial orientation framework has traditionally been applied to single firms, we argue that this framework can be of great value also when analyzing the overall entrepreneurial orientation of firms in an industry as a whole. This approach is particularly relevant in the antibiotics industry since it is characterized by the aggregate of a few important actors that all face similar challenges. What this essentially means is that in an industry facing strong environmental contingencies, the relationship between entrepreneurial orientation and performance becomes very similar across firms since the most powerful factors are these environmental contingencies. Thus, the analysis becomes one of the "collective" entrepreneurial orientation of all firms and the performance of the industry at large, as moderated by environmental contingencies. This is also what makes understanding the lack of entrepreneurial orientation a particularly relevant focus when considering the possibilities of reviving the antibiotics industry.

The entrepreneurial orientation of an industry as a whole is manifested through the actions of the main players in this industry with regards to developing their activities through innovation, expansion of activities or as new entrants into the industry. Another way of thinking of entrepreneurial orientation is as a proxy for the health of an industry; i.e., whether firms are investing, innovating, expanding and entering or, contrastingly, if they are drawing down activities and investments and are exiting. The central elements to the entrepreneurial orientation of firms in a particular industry are their predisposition to take action autonomously to innovate, to take risks, and to act proactively to business opportunities (Covin and Slevin 1988, 1989; Lumpkin and Dess 1996). Each one of these elements may characterize a firm's attempts to engage in an established market with innovative or existing products or services, and thus manifest its entrepreneurial orientation.

By capturing the tendency of the main players to innovate, take risks, and act proactively to seize business opportunities, entrepreneurial orientation can be seen as reflecting the health of an industry as judged by the behavior of its main players in terms of introducing new, innovative or existing, product or services. This because in doing so, these main players reinvigorate the market.

The basic relationship in this literature is thus that entrepreneurial orientation leads to firm performance (e.g. Brouthers et al. 2015; Lee et al. 2001; Teng 2007). Firm performance in turn, can be measured in terms of for example growth in sales, market share, or profitability. The main relationship between entrepreneurial orientation and firm performance is thereby that firms which are innovative, risk taking, and proactive reap the rewards of higher performance, which is what then allows for a healthy, and thereby attractive, industry as the key players are making profits or at least growing their sales.

However, this relationship is moderated by contingencies that may emanate from either the firm itself or from the business environment (Bowen and De Clercq 2008; Covin and Slevin 1989; Lumpkin and Dess 1996; Wales et al. 2013). More

specifically, there are a few particularly influential environmental factors that act as external contingencies on the relationship between entrepreneurial orientation and firm performance—and thereby are seen as requirements for a healthy industry. Research emphasizes the influence of the factors referred to as dynamism (Lumpkin and Dess 2001), munificence (Lumpkin and Dess 1996), and environmental hostility (Covin and Slevin 1989). These contingencies, which are of critical importance to the relationship between entrepreneurial orientation and firm performance, will be further elaborated on below.

First, the dynamism of an industry has been found to influence the relationship between entrepreneurial orientation and firm performance in that industry (Lumpkin and Dess 2001). In essence, the dynamism of an industry reflects the uncertainty experienced by firms, i.e., the extent of unpredictable or uncertain change that occurs in particular business environments (Child 1972). Uncertainty, in turn, undermines the ability of managers to adequately predict and plan for future events although they may be critically important for the firm (Alvarez and Busenitz 2001).

Environmental munificence can be understood as the overall profitability and growth in an industry. Entrepreneurial orientation in a munificent industry is claimed to have a stronger effect on firms' performance (Lumpkin and Dess 1996) as the munificence essentially suggests that there is space to grow and money to be made in the first place. Firms active in a munificent industry can thereby reap greater profits which in turn create a degree of slack that can be used to innovate, starting a benevolent spiral for the industry (Bourgeois 1981).

Finally, Covin and Slevin (1989) found how hostile environments, i.e., industry contexts characterized by intense competition, an unforgiving business climate, and a relative lack of exploitable business opportunities moderated the relationship between entrepreneurial orientation and firm performance. A hostile environment has this moderating effect because a starved industry resource base could inhibit innovation and experimentation (Bourgeois 1981) as well as create a focus on the conservation of scarce resources, such as the shrinking of R&D departments, and a focus on existing, rather than innovative, goods and services (Chakravarthy 1982; Covin and Slevin 1988; Teng 2007). Given these hostile industry environments, entrepreneurship and innovation would dwindle and the few new entries undertaken would risk suffering from a lack of sufficient resources to be successful (Lumpkin and Dess 1996). Taken together, the scarce resources characterizing a hostile industry environment would negatively moderate the link between entrepreneurial orientation and firm's performance. Hostility can thereby be understood as reflecting a scarcity of resources as well as a high intensity of competition for these (Covin and Slevin 1989; Zahra and Covin 1995) (Fig. 2).

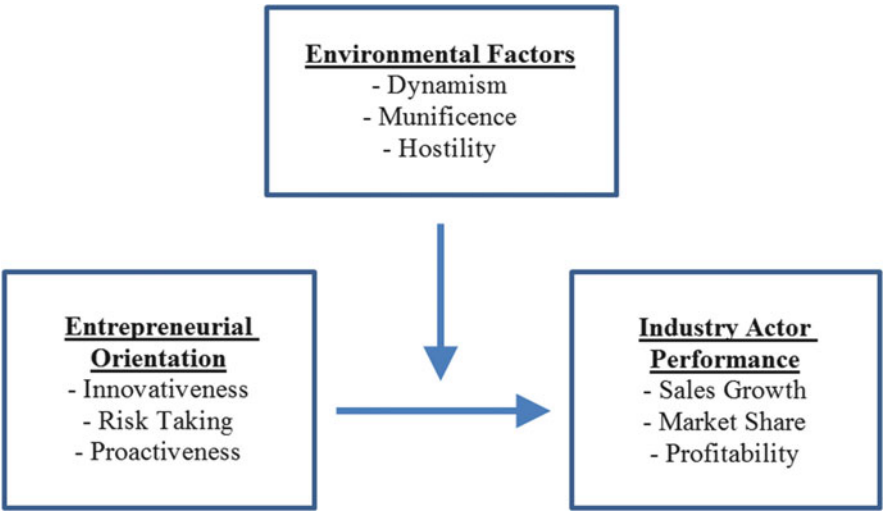

Fig. 2 Conceptual framework of entrepreneurial orientation. Source: Adapted from Lumpkin and Dess (1996)

6 Analysis

Applying the entrepreneurial orientation framework to understand the difficulties facing the antibiotics industry as a whole, the challenges presented earlier can be analyzed through such a lens as follows.

6.1 Entrepreneurial Orientation

As previously mentioned, the entrepreneurial orientation of an industry is expressed in the decisions of the main actors of that industry in terms of developing their activities by innovating, expanding their activities or in the decisions of new actors to enter the industry. The entrepreneurial orientation of firms in a healthy, vigorous industry drives them to take action to innovate, to take business risks, and to act proactively on opportunities. Looking at the case of the antibiotics industry, the entrepreneurial orientation of the actors is decidedly low. Rather than investing, innovating, expanding, or entering, firms are drawing down their activities and investments, closing labs, and are exiting the antibiotics industry.

6.2 Industry Actors Performance

The performance problems in the antibiotics industry are clear and numerous. We can see how the revenues from sales of existing antibiotics are down. We can also see how forecasting the sales of potentially new antibiotics are problematic since a new drug might be subject to minimal use to preserve its effectiveness for future resistance development. Furthermore, the market shares of many drugs are compromised by competition from generic drugs while the market is itself partly shrinking due to stewardship by hospitals and governments. Profitability in the antibiotics industry is overall very low, there have been a few "blockbusters" in the last couple of decades, but these are generally seen as unlikely to ever be repeated. Overall, the performance of the actors of the antibiotic industry is alarmingly low and very few players are still left in the industry as a consequence.

6.3 Environmental Factors

The environmental contingencies that most powerfully affects the antibiotics industry are, as we have learned from the received research discussed and illustrated above, the dynamism, munificence, and hostility of an industry.

First, the dynamism of the antibiotics market, i.e., the uncertainty and unpredictable future characterizing it, can be seen to be strongly affecting firms in the antibiotics industry. This dynamism is manifested through the uncertainty associated with antibiotics R&D, on the one hand, and with the unpredictability of the future markets for antibiotics that are being developed, on the other. There are high financial risks associated with antibiotics R&D. This as antibiotics R&D faces high and, importantly, increasing costs for clinical trials as well as long and increasing development time. For example, the difficulties in attaining enough patients in clinical trials create additional uncertainty in antibiotics R&D. It is today still particularly difficult to evaluate the resistance potential in bacteria and drug, and as a consequence this causes uncertainty in the development of antibiotics. There are substantial biological uncertainties in antibiotic R&D that make such efforts increasingly unpredictable and which require further attention from microbiology research, e.g. the ability of an antibiotic to successfully enter a bacterium, that it is not readily pushed back out, and that it is only toxic to the bacteria. There is moreover particularly high uncertainty surrounding the market for new antibiotics. It is difficult for a developer to estimate the future market due to the fact that resistance as well as the rate of infections can change quickly. As a consequence, validating the commercial potential of a promising molecule is challenging as it makes it hard to predict how big the health need will be at an early stage of development where major investment decisions need to be made. Additionally, there is considerable violation of intellectual property rights with regards to antibiotics which creates heavy price competition from both legal and illegal generic drugs. Taken together, the dynamism

of the antibiotics industry seems to pose challenges to firms through the uncertainty surrounding both antibiotic R&D and the forecasting of future markets for new antibiotics.

Second, the munificence of an industry is another of the main environmental factors influencing the relationship between entrepreneurial orientation and firm performance. This is expressed through the overall profitability or growth of an industry. Looking at the antibiotics industry, we can unfortunately see little of either. Rather, this industry is characterized by a lack of commercial attractiveness and low profitability among firms active in the field. We moreover see that there are low prices on antibiotics. Although difficult to generalize, research suggests that most antibiotics generate annual revenues that fall short of adequately covering their cost of development. Adding to this is the fact that the average annual growth of the market for antibiotics was 4% over the years 2005 to 2010—which is less than a quarter of the rate by which other major therapeutic areas grew. Large and effective antibiotic education campaigns have resulted in a reduction in antibiotic use and are thereby also thought to decrease the sizes of future markets for new antibiotics. But not only antibiotic stewardship is limiting future markets, also the development of antibiotic resistance is shortening the clinical lifespan of new antibiotics with resulting smaller overall markets for new antibiotic drugs. In sum, the munificence of the antibiotics industry is close to non-existent, featuring low prices, little profitability, and shrinking markets for new drugs.

Third, and lastly, the hostility of the industry environment is the third environmental factor found to influence the relationship between entrepreneurial orientation and firm performance. This hostility is manifested in a combination of intense competition and a lack of exploitable business opportunities. What we can see in the example of the antibiotics industry is that there is significant competition in a relatively saturated market. But this is not so much a consequence of healthy competition between efficient firms, or because there is little need for antibiotics, rather this is the effect of limitations on the pricing of antibiotics by governments reimbursement rules for such drugs. It is also because it is difficult to get onto the formularies from which doctors prescribe—i.e., becoming the prioritized treatment—because use is being discouraged, and because of competition from generic (off-patent or pirated) antibiotic drugs remains strong. Furthermore, many reimbursement systems encourage the use of the cheapest drug available. Taken together, most healthcare payers are today not prepared to reimburse antibiotics at the kind of prices which would act as incentives for antibiotic drug development. Concerning the lack of exploitable business opportunities, it has already been emphasized that it is hard to find new antibiotics. It has been said that "the low-hanging fruit" has already been picked in the antibiotics industry and the remaining opportunities will not be as scientifically easy to successfully pursue. However, and arguably equally as important, it is not easy to pursue those opportunities from a financial, or business, standpoint either, as a there is considerable hesitation from investors to fund antibiotics research, and, as a consequence, many valuable projects are believed to never have gotten off the ground. All in all, a hostile business environment is clearly

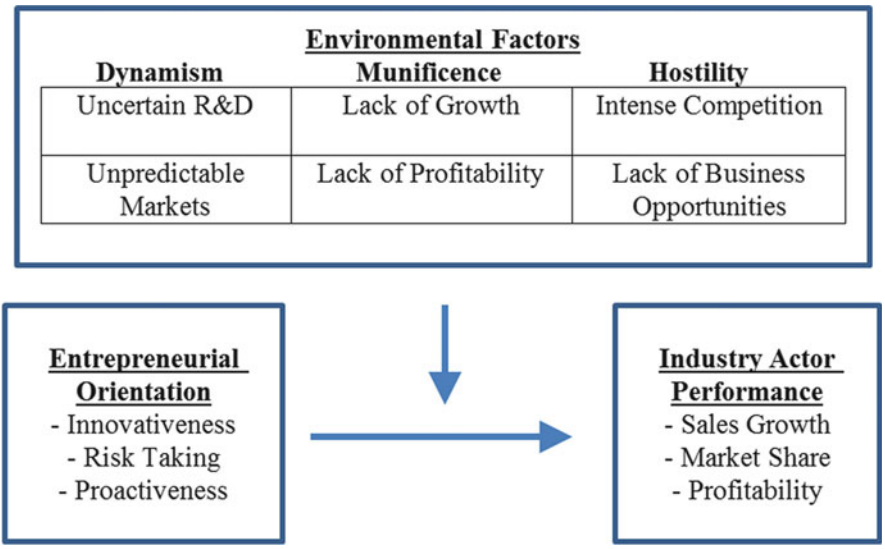

Fig. 3 Environmental factors within the framework of entrepreneurial orientation. Source: Own elaboration of Lumpkin and Dess (1996)

a salient feature of the antibiotics industry, with intense, but artificial, competition as well as few opportunities that makes "business sense" to pursue (Fig. 3).

6.4 Public Interventions

Applying the entrepreneurial orientation framework, we can see that the main environmental factors that constitute challenges facing the antibiotics industry are: the dynamism (the uncertainty and unpredictability of antibiotic R&D and future markets), the munificence (the growth and profitability of antibiotics as a field), and the hostility (the intensity of competition and lack of business opportunities in antibiotics). So, having established what several of the main problems facing this industry are, the focus now turns to what public policy interventions such as targeted grants and market entry rewards might do about these. Using the entrepreneurial orientation framework to evaluate how the suggested public interventions address, or fail to address, the environmental contingencies discussed above lead us to two key considerations.

The first consideration we want to make is if public interventions can act as antecedents of entrepreneurial orientation. In other words, is it possible for public intervention to boost firms' innovativeness, risk taking behavior and proactiveness? If this is possible, can we then argue for the inverse relationship between "performance" and "entrepreneurial orientation"? With the latter question we want to

explicitly address the potential effects of a sudden increased performance (due to public intervention) on the degree of entrepreneurial orientation of the industry.

The second consideration we find worth highlighting is how different public interventions (in our case grants and MER) can not only target environmental factors, but also have different impact on the entrepreneurial orientation—performance relationship. Although, we don't know what in practice will happen in the antibiotic industry once these interventions are in place, we can still conceptually consider the differences between the two interventions and what the impact may be if they are introduced. This is represented in the figure below illustrating how public intervention (grants and MER) may affect Environmental Factors (Dynamism, Munificence and Hostility), Industry Actors Performance and indirectly Entrepreneurial Orientation.

Now, let's turn to the differences between targeted grants and MER as means of public intervention to better understand their potentially different impact on the environmental contingencies weighing on the actors of the antibiotic industry and, if successful, the overall long-term entrepreneurial orientation of an industry.

6.5 Targeted Grants

Targeted grants have the benefit of reducing the early costs of developing a new antibiotic. This is important since the considerable challenges of antibiotic R&D otherwise may make these early investments prohibitively risky. From the perspective of the entrepreneurial orientation framework, this can be seen to have three potential effects.

First, by lowering the risk of investing in R&D, it helps to mitigate some of the financial uncertainty of this kind of investment. This suggests that we can understand targeted grants as essentially de-risking the investment for the firms as the grants picks up a piece of the cost in their cost/benefit analysis. This in turn would then mitigate (albeit only marginally) the challenges caused by the Dynamism and more specifically by the uncertainty characterizing antibiotics R&D.

Second, it can moreover be seen as affecting the Munificence contingency factor of low profitability. It does so in the sense of not improving revenues, but in lowering costs and thereby improving the cost/benefit analysis of firms considering whether it is profitable to invest in antibiotic R&D.

Third, by infusing potentially cash-strapped firms with capital enough to proceed through the next step of development, a targeted grant may also incentivize development in small- and medium-sized firms where antibiotics do not need to compete with other therapy areas for funding. In doing so, the targeted grants essentially address the Hostility contingency factor of intense competition. That said, the targeted grant does little for the intense competition from generic producers and slow uptake of new drugs in the antibiotics market.

All in all, targeted grants can be thought to have a number of very possible effect on the contingencies weighing on antibiotic developers in that it targets the costs and

financial risk of engaging in this activity as well as the scarcity of funds in firms already committed to further engagement. However, a public intervention relying on targeted grants does not seem to be able to mitigate the negative influences of the contingency factors of market uncertainty (Dynamism), low growth (Munificence), or lack of business opportunities (Hostility).

6.6 Market Entry Rewards (MERs)

A MER has the benefit of providing assured revenues for firms bringing new antibiotics of certain kinds to the market. This, in turn, can be thought to affect the environmental contingencies impeding antibiotic R&D in a number of ways.

First, a MER can be seen to create business opportunities in an industry which is desperately lacking these. In essence, that is what a MER is supposed to be—a business opportunity that is attractive enough to spur pharmaceutical firms into action of developing new drugs. In doing so, the MER can be seen to mitigate the Hostility contingency of lack of business opportunities.

Second, the MER can also be seen to provide certainty by essentially constituting a strong "customer" in a market that has been desperately lacking customers willing to pay enough for new antibiotics. In this sense, the MER can be understood to address the Dynamism contingency of uncertain markets. This is because it helps to correct some of the man-made market distortion that are creating such uncertainty about future markets for novel antibiotics. Being delinked in itself allows the MER to have an important effect in mitigating the environmental factors of dynamism, specifically the uncertainty brought on by the challenge of forecasting future markets for new antibiotics. Thereby a MER can be understood as potentially canceling out an important contingency that is weighing on the antibiotics industry by removing the generally considerable uncertainty surrounding future markets which in turn negatively influences investment decisions.

Third, a MER can be understood to influence the contingencies affecting antibiotic R&D by strongly increasing the profitability of antibiotics, or at least the ones targeted by the MER. By doing so, the MER can be expected to mitigate also the Munificence contingency of lack of profitability.

Fourth, by introducing a large payment in return for bringing new, much needed, antibiotics to market, the MER also addresses two aspects of the Hostility contingency of intense competition. One the one hand, it makes antibiotic projects that target the bacteria asked for by the MER more competitive internally, as the revenues from a MER could be even more than that expected from a drug in other therapy areas. On the other hand, the MER also allows a firm to essentially side-step the competition from generic producers and slow product uptake in hospitals by having a single "customer"; the public entity offering the MER, make one huge purchase of the rights for this antibiotic upon market entry, thus making competitors and hospital prescriptions irrelevant for the firms' revenues from this drug. This said, the introduction of a MER may create a different form of competition as different firms may

attempt to develop in parallel what could be seen as the same drug. How this might affect entrepreneurial orientation in the antibiotics industry is difficult to gage.

Although a MER can be expected to have a number of important effects, it does however not seem not to address the environmental contingencies of uncertain R&D (Dynamism) and low growth (Munificence).

6.7 Combining Targeted Grants and Market Entry Rewards

Having discusses the individual effects of the intervention mechanisms of targeted grants and MER, we now turn to the questions of whether these two interventions can, and should, be combined in addressing the challenges facing the antibiotics industry.

There are, obviously, crowding-out effects in deciding on public intervention as spending more public funds on MER may require spending less on targeted grants (or vice-versa).

However, targeted grants and MER may also complement each other. The value of combining both targeted grants and MER is that the targeted grants can be seen as having an effect earlier in the development of an antibiotic as compared to the MER, which shows effects much later in this process. Thus, if targeted grants are given to firms developing early-stage antibiotics, there may be more antibiotics having survived late enough in development to be targeted by the MER. In essence, this suggests that certain levels of grants are needed for a MER to work efficiently as it is based on the assumption that there are enough promising late-development antibiotics to target.

In addition, there could potentially be synergies between targeted grants and MER that could allow combing them to have an effect that is more than the sum of their parts. Synergies might be possible to achieve in the sense that one of the main problems facing the antibiotics market seem to be that related to Dynamism—i.e., that there is crippling uncertainty and unpredictability in regards to both the R&D and the future markets for antibiotics. Although these two kinds of challenges are related, solving one does not solve the overall problem of uncertainty. This, in turn suggests that targeting both of these uncertainties at the same time would have a considerably more powerful effect on incentivizing antibiotics R&D than would targeting only one of them. Additionally, we need to account for the fact that grants are provided early in the R&D effort, while MERs come into play effectively only after several years of innovation (i.e., when the new antibiotic enters the market, which typically can be after 6–10 years of development time). Thus, we highlight also the importance of looking at potential effects of combined public interventions in time.

Figure 4 illustrates of how public interventions may influence the entrepreneurial orientation of the antibiotic industry as well as address environmental contingencies holding it back. The factors that are potentially influenced by the Targeted Grants are *italicized*, and the ones influenced by the MER are grey and **bold**. The gray dashed

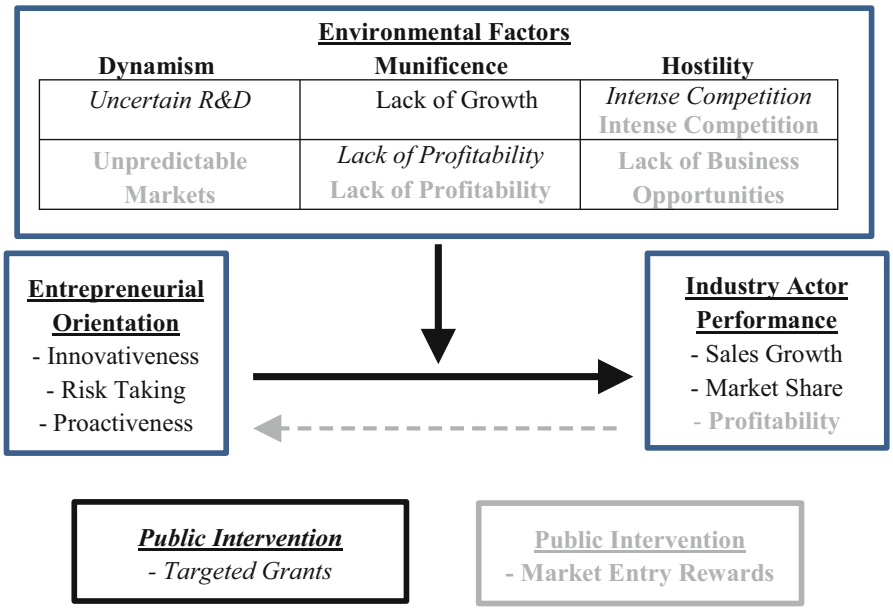

Fig. 4 Influence of public intervention on entrepreneurial orientation. Source: Own elaboration of Lumpkin and Dess (1996)

arrow illustrates the potential indirect impact of the MER on the entrepreneurial orientation—performance relationship.

7 Concluding Discussion

This chapter provides is a unique case of an important industry in health—the antibiotics industry—that is in rapid decline. This is an unusual setting as there is high demand for new antibiotics but low interest from companies to pursue the development of new ones. Combining the critical need for new antibiotics with the lack of innovation in the antibiotics industry suggests a clear proposition for public intervention to try to fix this industry. In this chapter, we outline not only the challenges facing the antibiotics industry but also two main public interventions that are currently being discussed to address the industry's decline.

Analyzing both the challenges and the suggested public interventions through the lens of the Entrepreneurial Orientation framework allows us to evaluate not only what the problems are, but importantly also how the public interventions may, or may not, address these problems and revive the antibiotics industry. In this sense, we found both promising effects and overlooked problems, and that there are important potential synergies between the public interventions discussed, which suggests they may need to be implemented in combination.

Above and beyond managerial and policy making implications, our discussions have also given rise to a number of interesting questions for theory and research on entrepreneurial orientation. For example: can public interventions influence the entrepreneurial orientation of an industry and, if so, how? Our analysis suggests that there could be reverse causalities in the relationship between entrepreneurial orientation of firms in an industry and the performance of the same. This suggests that if you can help make firms in an industry characterized by low collective entrepreneurial orientation more profitable, this could, by the extension of the entrepreneurial orientation framework, lead to increased innovation and entrepreneurial activities.

This study has a number of limitations. It is a study of a single industry yet which seeks to generalize conceptually to theory. Moreover, the study is based on a literature review of challenges to the antibiotics industry and this has no primary data that can verify if and to what extent these challenges are indeed correct. Additionally, and along the same lines, we are not able to say which challenges are more or less important for firms and why—a question that is of paramount importance for managerial practice and policy making alike.

Moreover, we left two types of environmental contingencies rather unaddressed (low growth and uncertainty of R&D), which will require further research. Although one line of thinking about such attempts at future research is that both these contingencies are not possible to address using public intervention; for example, how could we frame the relationship between uncertainty of R&D and money spent on R&D? Or, could we expect to reverse the lack of growth of the antibiotics market when stewardship is both on the rise and important? These are difficult questions; but one way to address these two contingencies could be to think of them not as direct moderating effects, but indirect ones. By this we mean that the uncertainties surrounding antibiotics R&D might not be possible to pay off, but perhaps the consequences of this uncertainty, in terms of higher failure rates, costlier projects, pickier investors, etc. could be addressed by using public interventions. Likewise, although growth may never return to the antibiotic industry in the traditional sense, due to stewardship and resistance, the market could still be expanded using public funds as long as there is a critical and concrete clinical need.

A final avenue for future research coming straight out of the results of this study is the consequences of somehow substituting traditional internal and external competition with a competition for MERs. How such a change would affect the industry and the firms' business models is to our knowledge unexplored and potentially problematic as this kind of solution might cause new challenges.

While there can be no certainty that the suggested public interventions for the antibiotic industry will work as intended, they can, from an Entrepreneurial Orientation perspective, be understood as attempts to essentially reverse the "entrepreneurial orientation—performance" relationship by creating profitability that is hoped to entice companies to start acting entrepreneurially again. This is an important theoretical contribution in the sense that it suggests that the entrepreneurial orientation framework is not so much one-way, as described in received research, but a dynamic framework where external factors may act not only on the main

relationship, as moderating factors, but also (in the case of public intervention) directly on the dependent variable of Industry Actor Performance. This, in turn, may suggest that the main relationship of the framework could be reversible and that decline in important industries is far from inevitable. However, if, and under what conditions, this is correct needs to be established by further research and possibly across different industries and countries.

Specifically, we see the possibility to act on entrepreneurial orientation by acting on the market side (e.g., a MER) as long-term results if the number of successful innovations is high enough to create a healthy antibiotics R&D pipeline. At such point in time, when more firms will be attracted (again) to the industry, it could be possible to consider taking away public interventions. Such instance would be also a very interesting object of study for future research. Specifically, from a longitudinal perspective would be interesting to study the criteria and effects of introduction and subsequent elimination of public interventions from an industry. Future research should also devote some efforts to conduct cross industry analysis of public interventions effects on collective entrepreneurial innovation in the attempt to find more generalizable factors in terms of effects of public interventions.

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