Research Synthesis: Role of Small and Medium-sized Enterprises

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Introduction

The literature around small and medium-sized enterprises (SMEs) in pharmaceutical innovation is considerable*, with most of the discussion focusing on R&D share of SMEs and Emerging Companies. Most of the literature seems to have been produced from 2005 onwards.

Search terms

"small and medium-sized enterprise", "SME", "small pharmaceutical companies", "small" and "companies" or "biotechnology"; "firm size" with/without "biomedical"; "pharmaceutical" and "innovation" or "research" and "development".

Synthesis of the literature

Definitions

The literature uses various definitions for the term "small and medium-sized enterprise (SMEs)", usually based on revenues and/or employee count. Some authors also further differentiate SMEs from what is referred to as "emerging" pharmaceutical or biotechnology biotech companies, but most papers include those in the definition of SMEs. For example, BIO used the term "emerging therapeutic companies" (ETCs) to refer to those that are "a) developing therapeutics with a lead drug in R&D, or b) have a drug on the market, but have less than $1 billion in sales at the time of the transaction" (Thomas 2019). Hay et al. used the term "emerging biotech" for those companies that have less than $0.1 billion in sales (Hay et al. 2014).

The following are examples of definitions based on:

1. Revenues:
    - Below $1 billion in gross revenues (T. J. Hwang, Carpenter, and Kesselheim 2014; Thomas J. Hwang and Kesselheim 2016).
    - Between $0.1-5 billion of sales (Hay et al. 2014).
    - Below $100 million in sales for small biopharma companies and between $100 million and $1 billion for mid-sized biopharma companies (Geilinger and Leo 2019).
    - Between $500 million to less than $5 billion in annual "global prescription sales" (IQVIA 2019b) for SMEs and less than $500 million in sales or with less than $200 million of research and development

expenditures per year for "emerging biopharma companies" (EBCs) (IQVIA 2019b).
- Between $100 million and $3 billion in annual revenues for "emerging biopharma companies" (The Boston Consulting Group, cited by Brouwers, Garrison, and Barido 2011).
- "Not more than €50 million in turnover or €43 million on the balance sheet" (European Union, Commission Recommendation 2003/361/EC, cited by Lincker et al. 2014).

2. Employee Count:
   - Employee count of 100 or less as SMEs (Moran et al. 2007).
   - Companies "[w]ith < 1,000 employees at time of drug discovery" (Kneller 2010)
   - "Headcount [of] less than 250" (European Union, Commission Recommendation 2003/361/EC, cited by Lincker et al. 2014).

As may be gleaned from these examples, the literature does not adopt any standard definition for SMEs and vary widely in their criteria, whether based on revenue, employee count or both. It is also noted that SMEs and EBCs/ETCs sometimes have overlapping definitions.

Characteristics and Advantages

SMEs are generally characterized as being externally funded, with a flexible structure and a higher degree of risk taking compared to large firms. Kaitin notes the changing trend within the pharmaceutical industry with respect to the R&D process - from the long-standing model of "a fully integrated pharmaceutical company model of R&D" wherein individual pharmaceutical companies are responsible for the entire drug R&D process to "a fully integrated pharmaceutical network" which utilizes the capabilities of all the relevant R&D actors, including the "small pharmaceutical and biotechnology companies" (Kaitin 2010). These small companies are described to be primarily reliant on external R&D funding, coming from sources such as venture capital or large companies, with substantial amounts of debt and limited numbers of products already on the market. However, these companies are seen by their larger counterparts to be more adaptable, able to take more risks and have a less rigid structure. These characteristics thus, allow them to "focus on emerging technologies and on developing highly innovative therapeutics" and has led to increasing collaborative projects with and takeovers by large companies (Kaitin 2010). Small biotech companies have also been observed to pursue drug targets deemed to be of higher risk and "less validated." As compared to their larger counterparts, they are said to "more likely to have less experienced development teams and fewer resources" (Hay et al. 2014).

Gopalakrishnan and Bierly examined the "knowledge strategies" of 27 drug delivery-focused companies - 17 of which were categorized as small firms (having less than or equal to 500 employees) and 10 firms classified as large (having more than 500 employees). Among other observations made in the study, they found that the small firms' ability to quickly adapt into their products or processes the latest available technologies ("learning speed") was crucial for them to be able to obtain higher volumes of patents and citations ("technological strength"), as compared to their large counterparts, They noted that this observation is in line with results from prior studies that "speed and flexibility" are some of the main advantages that small companies have over large companies (Gopalakrishnan and Bierly 2006).

R&D share and contributions

SMEs and EBCs are increasingly being recognized for their growing R&D contributions, especially in the U.S.

1. General R&D

In 2019, ETCs, on their own or with partners, were said to be responsible for 73% (5,067 out of 6,984) of the total global "industry" drug clinical-stage projects, with the remainder done by large companies. Disaggregated, ETCs would account for 71%, 76%, 68% and 62% of Phase I, II, III and new drug applications, respectively, as compared to those done by large companies. 45% of all ETC clinical-stage pipeline projects are conducted with other partner companies. Oncology is the top disease focus for these ETC clinical projects (Thomas 2019). In 2018, IQVIA identified that there are 74 small companies that have combined global sales of $159 billion and 446 drugs in their R&D pipeline, 9 mid-sized companies with $50 billion sales and 181 products, and 3,212 emerging biopharma companies with $139 billion sales and 8,752 products. In comparison, 25 large companies had combined annual sales of $637 billion and 1,845 products. Comparing data between 2003 and 2018, EBCs were observed to have an increasing share of early-stage product pipelines (encompassing discovery until Phase I stages) from 68% to 84%. In 2003, there were 1,383 products identified globally in the late-stage phase (encompassing Phase II until registration stages) and this number increased to 2,891 in 2018. Again comparing data between 2003 and 2018, EBCs were also observed to have an increasing share of late-stage product pipelines from 52% to 73%, respectively. During the same period, small and mid-sized companies were observed to have a limited and decreasing share of late-stage product pipeline of 6% to 5% and 5% to 3%, respectively. The large companies also exhibited a similar decreasing trend for late-stage product pipeline from 36% to only 19%. The increased share of pipeline products from EBCs were attributed to their sizable involvement in oncology and orphan drug R&D activities (IQVIA 2019b).

According to the 2017 BIO Industry Analysis, small biotechnology companies are responsible for 70% of all biopharmaceutical clinical trials worldwide amounting to 6,679 programs, 43% of which were conducted in partnership with another company. The remaining 30% of these clinical trials were being conducted by large companies (Biotechnology Innovation Organization n.d.).

Using information contained in the BioMedTracker database, Hay et al. examined the success rates in clinical development of 4,451 investigational drugs in the U.S. belonging to 835 companies and involving 5,820 phase transitions during the period of 2003 to 2011. Looking closely at the composition of the drug developers, 4% were large pharmaceutical companies or biotechnology companies developing 47% of these investigational drugs, 11% were small to mid-sized pharmaceutical companies or biotechnology companies developing 16% of these drugs and 85% were emerging biotechnology companies developing 37% of these drugs. They found, among others, that only 10.4% of the 5,820 "indication development paths in phase 1 were approved by FDA." In explaining their "lower success rates" results as compared to other studies, they noted as a contributing factor the sizable representation of small biotech companies. Funding limitations were also identified to have influenced the small companies' drug development choices (Hay et al. 2014).

2. Disease and technology specific

Hwang and Kesselheim analyzed clinical trials for vaccine development from the Pharmaprojects database of

Informa from 1990 to 2012. It was observed that 71% of new vaccine Phase I trials, globally, were initiated by SMEs as compared to 38% of Phase III vaccine trials, which had more involved of larger companies. Looking at disease specific vaccines, 69% of Phase I trials focusing on HIV, malaria, tuberculosis and tropical infectious diseases' vaccines were attributed to SMEs (Thomas J. Hwang and Kesselheim 2016). In a 2007 study, Moran et al. found that SME-led vaccine clinical development for malaria comprised 13% of all clinical projects in 2006, with the rest conducted by public-private partnerships (PPPs) and public institutions, accounting for 25% and 62% respectively. This is different from 1995 when malaria clinical projects were undertaken only by PPPs, public institutions and multinational companies. In relation to malaria drugs, in 2006 SMEs had a 10% share of the global development portfolio and the remainder done by product development partnerships (47%), public institutions (24%) and multinational companies (19%) (Moran et al. 2007). For the Seventh EU Framework Programme on Human Vaccine Research, it was observed that the vaccine projects had private sector partners accounting for greater than 13% of the total number of project partners, specifically comprising of SMEs (39 partners) and large companies (5 partners). It was also noted that clinical trials for DNA vaccines are mainly sponsored by SMEs and not by large companies. Sautter et al. noted the importance of enticing pharmaceutical industry players, particularly SMEs, to "boost [vaccine] innovation and translational research" in the EU (Sautter et al. 2011). Similarly, for antibiotic R&D efforts, SME clinical trial efforts have increased from below 30% in 1990 to 60% in 2012 (T. J. Hwang, Carpenter, and Kesselheim 2014).

As of December 2004, Moran et al. identified 29 out of 63 public-private partnership ("PPP") projects focusing on drug R&D for neglected diseases that employed "small-scale commercial firms and academics/public groups working on a fully paid basis." Of these 29 projects, 4 were identified to be done by "small companies focused on neglected diseases" and another 4 done by "small companies focused on Western diseases," all of which are Western-based. The former group views neglected diseases as a "potential commercial niche market" and as such, they do not rely on PPP funding but rather expect to obtain monetary gains for actual sale of their products. The latter group, by specializing on Western markets, rely on financing from venture capitalists and are thus, pressured to produce profits which the neglected diseases market do not offer. For both groups, PPPs can offer financing and technical expertise, however these are said to be needed to a much greater extent by the latter considering that it still needs "catalyzing" agents to engage in neglected disease R&D activities (Moran et al. 2005).

3. Drug Approvals

Geilinger and Leo noted that, in 2018, 49% of U.S. drug approvals were owned or being licensed by smaller companies with sales amounting to $100 million or less as compared to the 25% share of the 10 pharmaceutical companies generating the topmost sales worldwide (Geilinger and Leo 2019). Kneller traced 252 U.S. Food and Drug Administration (FDA) approved-drugs between the period of 1998 to 2007 (this number reflects "almost all" the FDA-approved and Center for Drug Evaluation and Research-regulated drugs within the said period) and studied the involvement of different inventors during the drug discovery process. He concluded that the drug discovery levels by small companies are almost comparable to the large pharmaceutical companies. It was also noted that 18% of the 252 total drug base was discovered by biotechnology companies. (Kneller 2010).

Munos examined the origins of 1,222 FDA-approved new molecular entities (NMEs) between 1950 to 2008. He found, among others that: (i) 193 of these NMEs were developed by 103 small companies that were subsequently merged or acquired and thus, no longer exists; (ii) 25 were developed by 19 already-liquidated

small companies; (iii) 79 were developed by 23 small companies that were active from 1950 to 2008; and (iv) 105 were developed by 66 small companies that existed by virtue of merger or acquisition agreements. He further observed that small companies were responsible for an increasing share of U.S. FDA-approved NMEs, from just approximately 23% in the 1980s to almost 70% in 2008. In contrast, the share of NMEs originating from large companies had decreased from 75% to 35% during the same period. It was observed that, beginning 2004, "small companies have consistently matched or outperformed their larger competitors." This increased NME productivity from small companies had been attributed to the growing number of small companies with an NME and that small companies are increasing their "mean annual NME output." Analyzing projects in the discovery stage between 1980 to 2004, small companies accounted for 47% of these which is a greater share as compared to only 38% from large companies. However, small and large companies were noted to have almost an equal share of projects in the development stage for the same period (Munos 2009).

For 59 "new active substances" submitted for approval with the U.S. FDA in 2018, IQVIA observed that 64% of these were invented by EBCs, another 5% each by small and mid-sized companies and 25% coming from large companies. For the submission of these 59 substances with the FDA, 47% were done by EBCs, and the large companies coming close at 44% and the remaining 5% and 3% made by mid-sized and small companies respectively (IQVIA 2019a). It was also observed that the active ingredient of approximately 22% of the 50 leading drugs in 2009 were discovered or created by EBCs (Brouwers, Garrison, and Barido 2011).

Further, Mullard noted the growing role of small "emerging sponsors" – referring to first-time recipients of U.S. FDA approvals - in drug development efforts. They were observed to be responsible for 41% of the drug approvals in 2012, and 37% in 2011. There were six emerging sponsors in 2012 and four in 2011 who independently obtained FDA approvals (Mullard 2013). Lincker et al. looked at 94 medicinal marketing authorization applications with a "new active substance" that received approval from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use during the period of 2010 to 2012. They found that 27% of these approved applications and 61% of applications dealing with orphan drugs originated from SMEs. Also, 13% of these had SMEs as the "marketing authorization holder." Looking at the transfer of products among developers, they observed that 18 applications originated from SMEs that were eventually transferred to large or "intermediate" companies, majority of which took place by virtue of out-licensing agreements (13 applications) and the rest (5 applications) resulted from a merger or acquisition agreement with a large company. SMEs were also the recipients of these transfers from "academic/public bodies/PPPs" at 5%, large or intermediate companies at 4% and other SMEs at 2% (Lincker et al. 2014).

R&D Costs and Efficiency

There is limited research on the actual R&D costs incurred by SMEs. From the existing studies, it is unclear whether their costs are higher or lower than their larger counterparts. Myers and Shyam-Sunder estimated the risk values and capital costs as of December 1988 for seven "'small' pharmaceutical firms" and compared them to the corresponding values for large pharmaceutical firms. They observed that the small firms had higher risk values and capital costs than their larger counterparts (Myers and Shyam-Sunder 1996). Figures from 2005 from DiMasi and Grabowski showed the costs for research and development of seventeen biopharmaceuticals developed by four biotech firms (the definition of which was not provided in the study). Among others, they found that: (i) each approved biopharmaceutical will involve the following "out of pocket" estimated expenditures, USD 198 million for preclinical, USD 361 million for clinical and a total of USD 559 million, and

(ii) using data adjusted for time period differences, total biotech R&D "out of pocket" cost for each approved biopharmaceutical at USD 559 million is less costly than "traditional pharmaceutical firms" at USD 672 million [monetary figures are expressed in 2005 USD values] (DiMasi and Grabowski 2007).

Ardal et al. surveyed 25 SMEs (majority of which deal with "human health" but 28% of which also work on "animal health and/or environmental issues") in Europe as to the costs and time frames of antibiotic research and development (R&D), from lead compound identification to phase II clinical trials. They identified the following estimate costs and time frames: (i) during the identification phase for lead compounds, SMEs may incur costs between € 100,001 to greater than € 1,000,000 taking between 6 months to 4 years; (ii) during the optimization phase of lead compounds, many of the SMEs incurred or project to incur costs of € 1 – 5 million again within 6 months to 4 years; (iii) during preclinical trials, many of the SMEs incurred or project to incur costs of € 1 – 5 million within 1 to 2 years; (iv) during clinical – Phase I trials, many of the SMEs incurred or project to incur costs of € 1 – 10 million within 6 months to 2 years; and (v) during clinical – Phase II trials, many of the SMEs incurred or project to incur costs of € 1 – 20 million within 1 to 4 years. Their results were interpreted to indicate that SMEs anticipate to incur less R&D costs than their larger counterparts (Årdal et al. 2018).

R&D Challenges

Clinical development programs, especially in terms of their design and implementation, pose significant challenges for small biopharmaceutical companies. These are mainly attributable to constraints in finances, resources and limited experience. Moscicki and Tandon discussed four rare disease-drug development cases conducted by small biopharmaceutical companies and the approaches they used to overcome specific clinical program difficulties. They also provided a sample list of small biopharmaceutical companies who obtained drug approvals between 2014 and 2015 after conducting phase III clinical trials and the institutional strategies used by these companies to overcome drug development challenges, i.e. targeting only certain diseases, focusing on drug-repurposing or reliance on licensing agreements (Moscicki and Tandon 2017). Particularly for vaccine research and development efforts in the EU, the main challenges to SME participation as determined during the stakeholder discussions conducted by the Innovation Partnership for a Roadmap on Vaccines in Europe, are: skills and expertise acquisition, and funding availability (Medaglini et al. 2018). ten Ham et al. surveyed 271 for-profit companies involved in the European market (as of January 2017) on their development efforts for advanced therapy medicinal products on the challenges they faced in their clinical development efforts. Out of their 68 respondents, 65% were identified to be SMEs (having an employee count of between 1 to 249 individuals) and the remaining respondents were large companies. The authors noted greater SME involvement in advance therapy medicinal products than in "small-molecule and biotechnology industry." Challenges confronting SMEs working in this area include those related to preclinical translation and clinical development financing (ten Ham et al. 2018).

Strategies

1. Innovation

Several researchers have examined the innovation strategies of SMEs and ETCs. Wikhamn et al. surveyed 104 Swedish biopharmaceutical SMEs to determine the extent of industry awareness and employment of "open

innovation activities." Their study revealed that, among others, while open innovation is not a widely-known concept among the Chief Executive Officer - survey respondents, the majority of the SMEs were engaging in business practices that are aligned to this concept, for example "external networking" attributable to "standard [industry] practices." Further, they observed that the use of open innovation practices by SMEs within their own research and development departments was not intended to scale down these departments. Lastly, they noted that SMEs that employ open innovation strategies are deemed to be more innovative than their peers (Wikhamn et al. 2016). Prokop and Stejskal examined and identified the variables that affect "product and process innovations" of German SMEs. With respect to the "473 Chemical and Pharmaceutical" organizations included in the study, they found, among others, that for small firms (those that have an employee count of less than 50), the most influential variables for "innovation activities" are "in-house and external R&D activities and expenditures" (Prokop and Stejskal 2019).

2. Licensing Arrangements

Thomas showed that in 2018 ETCs out-licensed projects and received "upfront" fees totaling $9.1 billion from large companies. This reflects a 107% increase from the licensing activities in 2017, which only amounted to $4.4 billion. Between the years 2009 to 2018, the global average of acquisition deals involving ETCs, whether R&D or market-oriented, is 41 deals. The number of acquisitions in 2018 was slightly lower than the average at 32 deals, of which 66% involved U.S.-based ETCs and had a total value of $26.4 billion. 88% of these 2018 deals involved R&D-oriented ETCs with a total acquisition value of $32.5 billion and the remainder involved market-oriented ETCs with a total acquisition value of $2.2 billion (Thomas 2019). Song and Leker analyzed the licensing agreements of pharmaceutical companies in Korea in order to determine their use "to differentiate distinct innovation strategies." Among other things, the study examined "firm size" as one of the variables and noted that this has a positive influence on whether companies would enter into licensing arrangements. Further, they noted that the small Korean pharmaceutical companies included in the study only had a few licensing arrangements (Song and Leker 2019).

Incentives

Incentives for SME R&D efforts may include direct grants, tax credits and priority review vouchers.

1. Actual Incentives

A few papers analysed the financial incentives currently available for SMEs. The 50% tax credit for clinical trial costs, which was available to entities conducting drug R&D for rare diseases under the 1983 U.S. Orphan Drug Act, is said to have a positive effect on SMEs' survival and growth (T. J. Hwang, Carpenter, and Kesselheim 2014). To assist diagnostics-focused SMEs in the EU, the European Commission through its Horizon 2020 program made available € 130 million of funds for "clinical research for the validation of biomarkers and/or diagnostic medical devices." It was observed that this call received quality proposals from 1194 respondents (Sanne 2018).

Ekins and Wood discussed their experiences in setting up 2 U.S.-based small companies for "early stage" research efforts on rare and neglected diseases. Their companies sought federal funding from the Small Business Technology Transfer and Small Business Innovation Research programs of the U.S. National Institutes

of Health. They opined that the potential issuance of a FDA priority review voucher[1] for drugs on rare pediatric diseases may help their companies attract private investors such as venture capitalists "in the absence of a sizable patient population" for their target diseases (Ekins and Wood 2016).

With respect to financing, Thomas found that in 2018, global venture capital financing directed towards ETCs increased to $17.5 billion from only $4.4 billion in 2009. Particularly, U.S. based ETCs received venture investments amounting to $12.3 billion in 2018, 95% of which were intended for new R&D projects while the rest were allocated for drug improvement R&D efforts. These U.S. based companies received a significantly higher amount of venture funding compared to their non-U.S. counterparts, which received a total of $5.2 billion. U.S. and non-U.S ETCs focusing on R&D activities for oncology receive the most funding from venture capitalists (Thomas 2019).

2. Suggested Incentives

Another set of papers discussed incentives that could be made available for SMEs health product development. Noting their significant share in the conduct of Phase I vaccine trials as compared to large pharmaceutical companies, Hwang and Kesselheim suggested the enactment of policies – i.e. public-private partnerships and prize incentives - to assist the R&D efforts of SMEs in this area (Thomas J. Hwang and Kesselheim 2016). Similarly, Hwang, Carpenter and Kesselheim suggested that policy measures should target SMEs conducting antibiotics R&D to help them in their activities, i.e. through tax credit schemes, public-private partnerships and direct research funding (T. J. Hwang, Carpenter, and Kesselheim 2014).

Useful resources

1. Since 2015, BIO has published an annual report on global trends concerning ETCs, from funding to drug pipeline portfolio shares. The reports are accessible from this link: https://www.bio.org/bio-industry-analysis-reports.
2. The EMA's SME Register (found in this link: https://fmapps.emea.europa.eu/SME/search_advanced2.php) provides a searchable database of SMEs registered as such in the European Economic Area. Among others, the results can be filtered based on R&D stages in relation to (bio)pharmaceutical and medical device and technology sectors as well as by type of products, substances and therapeutic areas.

Research gaps

- Analysis on R&D contributions of non U.S.-based SMEs
- Analysis on R&D costs and efficiency incurred by SMEs

[1] There is a separate research synthesis on priority review vouchers, available at https://www.knowledgeportalia.org/priority-review-vouchers

Study Authors	SME Definitions	SME share in Pre-clinical	SME share in Clinical trial - Phase I	SME share in Clinical trial - Phase II	SME share in Clinical trial - Phase III	SME share in Drug Approvals
	1. Based on Revenues					
Geilinger and Leo 2019	- "Mid-sized biopharma companies": "[c]ompanies with significant sales of usually between $100 million and $1 billion" - "Smaller biopharma": "other smaller biopharma companies"					In 2018, 49% of U.S. drug approvals were owned or being licensed by smaller companies with sales amounting to $100 million or less as compared to the 25% share of the 10 pharmaceutical companies generating the topmost sales worldwide.
IQVIA 2019b	- "Mid-sized companies": having "between $5 to less than $10 billion annual sales" - "Small companies": having an annual "global prescription sales between $500 million to less than $5 billion"					

T. J. Hwang, Carpenter, and Kesselheim 2014	SMEs: having lower than $1 billion in gross revenues		For antibiotic R&D efforts, SME clinical trial efforts have increased from below 30% in 1990 to 60% in 2012.			
Thomas J. Hwang and Kesselheim 2016			The study analyzed the Pharmaprojects database of Informa for pharmaceutical products starting Phase I clinical trials from 1990 to 2012. As compared to their larger counterparts, it was observed that 71% of new vaccine Phase I trials, globally, were initiated by SMEs. 69% of Phase I trials focusing on HIV, malaria, tuberculosis and tropical infectious diseases' vaccines were also attributed to SMEs.		As compared to their larger counterparts, SMEs initiated 38% of Phase III vaccine trials.	
	2. Based on Employee Count					
Kneller 2010	"small established pharmaceutical companies": "[w]ith < 1,000 employees at time of drug discovery"					The study traced 252 U.S. FDA approved-drugs between the period of 1998 to 2007 (this number reflects "almost all" the FDA-approved and Center for Drug Evaluation and Research-

						regulated drugs within the said period) and studied the involvement of different inventors during the drug discovery process. It was observed that 7 of these drugs, mainly follow-ons and one that is under FDA priority review, were discovered by "small, established pharmaceutical companies." The study concluded that the drug discovery levels by small companies are almost comparable to the large pharmaceutical companies. It was also noted that 18% of the 252 total drug base was discovered by biotechnology companies.
Moran et al. 2007	SMEs: with employee count of 100 or less		The SME-led vaccine clinical development for Malaria comprised 13% of all clinical projects in 2006, with the rest conducted by public-private partnerships (PPPs) and public institutions, accounting for 25% and 62% respectively. This is different from the observations made in 1995 when malaria clinical projects were undertaken only by PPPs, public institutions and multinational companies. In 2006, SMEs had a 10% share of the global development portfolio for malaria drugs and the remainder done by product development partnerships (47%), public institutions (24%) and multinational companies (19%).			

	3. Based on Revenue and Employee Count					
Lincker et al. 2014	SMEs (based on European Union definition): having a "[h]eadcount [of] less than 250, and not more than €50 million in turnover or €43 million on the balance sheet"					The study looked at 94 medicinal marketing authorization applications with a "new active substance" that received approval from the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use during the period of 2010 to 2012. It was found that 27% of these approved applications and 61% of applications dealing with orphan drugs originated from SMEs. Also, 13% of these had SMEs as the "marketing authorization holder." Looking at the transfer of products among developers, it was observed that 18 applications originated from SMEs that were eventually transferred to large or "intermediate" companies, majority of which took place by virtue of out-licensing agreements (13 applications) and the rest (5 applications) resulted from a merger or acquisition agreement with a

						large company. SMEs were also the recipients of these transfers from "academic/public bodies/PPPs" at 5%, large or intermediate companies at 4% and other SMEs at 2%.
	4. SMEs including Biotech* * "Biotechnology companies": those post-1975 "drug discovery" companies "[s]ome of which are primarily engaged in small-molecule drug discovery, rather than protein therapeutics harnessing recombinant DNA technology" (Kneller 2010)					
Munos 2009	"small pharmaceutical companies": those companies that do not belong to the top 15 pharmaceutical companies as well as their predecessors and resulting joint ventures, and this also encompasses biotechnology companies	The study examined the origins of 1,222 FDA-approved new molecular entities (NMEs) from 1950 to 2008. In analyzing projects in the discovery stage between 1980 to 2004, small companies accounted for 47% of these projects, which is a greater share as compared to only 38% from large companies. However, small and large companies were noted to have almost				The study found, among others that: (i) 193 of these FDA-approved NMEs were developed by 103 small companies that were subsequently merged or acquired and thus, no longer exists; (ii) 25 were developed by 19 already-liquidated small companies; (iii) 79 were developed by 23 small companies that were active from 1950 to 2008; and (iv) 105 were developed by 66 small companies that existed by virtue of merger or acquisition agreements. It was further observed that small companies were responsible for an increasing share of U.S. FDA-approved NMEs, from just

		an equal share of projects in the development stage for the same period.				approximately 23% in the 1980s to almost 70% in 2008. In contrast, the share of NMEs originating from large companies had decreased from 75% to 35% during the same period. It was also observed that, beginning 2004, "small companies have consistently matched or outperformed their larger competitors." This increased NME productivity from small companies had been attributed to the growing number of small companies with an NME and that small companies are increasing their "mean annual NME output."
Hay et al. 2014	SMEs: having sales between $0.1-5 billion, and includes in this term biotech companies falling within this revenue category					
	5. Emerging companies					
IQVIA 2019b	"emerging biopharma companies" (EBCs):	EBCs were observed to have an increasing share of early-stage product pipelines (discovery until Phase I stages) from 68% to 84% in 2003 and 2018,		In 2003, there were 1,383 products identified globally in the late-stage phase (Phase II until registration stages) phase and this number increased to 2,891 in 2018. Again comparing data between 2003 and 2018, EBCs were also observed to have an increasing		

	as either (i) having annual sales of less than $500 million, or (ii) with less than $200 million of research and development expenditures per year	respectively.		share of late-stage product pipelines from 52% to 73%, respectively. Small and mid-sized companies were observed to have a limited and decreasing share of late-stage product pipeline of 6% to 5% and 5% to 3%, respectively, for the years 2003 and 2018.		
IQVIA 2019a						The study looked at 59 "new active substances" submitted for approval with the U.S. FDA in 2018. It was observed that 64% of these were invented by EBCs, another 5% each by small and mid-sized companies and 25% coming from large companies. For the submission of these 59 substances with the FDA, 47% were done EBCs, and the large companies coming close at 44% and the remaining 5% and 3% made by mid-sized and small companies, respectively.
Brouwers, Garrison, and Barido 2011	EBC as having "annual revenues between $100 million and $3 billion"					It was observed that the active ingredient of approximately 22% of the 50 leading drugs in 2009 were discovered or created by EBCs.
Thomas 2019	"emerging therapeutic companies" (ETCs): "a) developing therapeutics with a		In 2019, ETCs, on their own or with partners, were said to be responsible for 73% (5,067 out of 6,984) of the	ETCs would account for 76% of Phase II projects as compared to those done by large companies.	ETCs would account for 68% of Phase III projects as compared to those done by large companies.	ETCs would account for 62% of new drug applications as compared to those done by large companies.

	lead drug in R&D, or b) have a drug on the market, but have less than $1 billion in sales at the time of the transaction"		total global "industry" drug clinical-stage projects, with the remainder done by large companies. ETCs would account for 71% of Phase I projects as compared to those done by large companies.			
Hay et al. 2014	"emerging biotech" for those companies that have less than $0.1 billion in sales		Using information contained in the BioMedTracker database, the study examined the success rates in clinical development of 4,451 investigational drugs in the U.S. belonging to 835 companies and involving 5,820 phase transitions during the period of 2003 to 2011. Looking closely at the composition of the drug developers, 4% were large pharmaceutical companies or biotechnology companies developing 47% of these investigational drugs, 11% were small to mid-sized pharmaceutical companies or biotechnology companies developing 16% of these drugs and 85% were emerging biotechnology companies developing 37% of these drugs. They found, among others, that only 10.4% of the 5,820 "indication development paths in phase 1 were approved by FDA."			
	No SME Definition provided					
Biotechnology Innovation Organization (BIO) n.d.			According to the 2017 BIO Industry Analysis, small biotechnology companies are responsible for 70% of all biopharmaceutical clinical trials worldwide amounting to 6,679 programs, 43% of which were conducted in partnership with another company. The remaining 30% of these clinical trials were being conducted by large companies.			
Sautter et al. 2011			For the Seventh EU Framework Programme on Human Vaccine Research, it was observed that the vaccine projects had private sector partners accounting for greater than 13% of the total number of project partners, specifically comprising of SMEs (39 partners) and large companies (5 partners). The study also noted that			

			clinical trials for DNA vaccines are mainly sponsored by SMEs and not by large companies.			
Mullard 2013						The study noted the growing role of small "emerging sponsors" – referring to first-time recipients of U.S. FDA approvals – in drug development efforts. They were observed to be responsible for 41% of the drug approvals in 2012, and 37% in 2011. Further, there were six emerging sponsors in 2012 and four in 2011 who independently obtained FDA approvals.

Study Authors	SME	Large Companies	Others
Biotechnology Innovation Organization (BIO) n.d.	According to the 2017 BIO Industry Analysis, small biotechnology companies are responsible for 70% of all biopharmaceutical clinical trials worldwide amounting to 6,679 programs, 43% of which were conducted in partnership with another company.	The remaining 30% of these clinical trials were being conducted by large companies.	
Thomas J. Hwang and Kesselheim 2016	The study analyzed the Pharmaprojects database of Informa for pharmaceutical products starting Phase I clinical trials from 1990 to 2012. As compared to their larger counterparts, it was observed that 71% of new vaccine Phase I trials, globally, were initiated by SMEs, as compared to only 38% of Phase III vaccine trials. 69% of Phase I trials focusing on HIV, malaria, tuberculosis and tropical infectious diseases' vaccines were also attributed to SMEs.	Larger companies initiated 29% and 62% of the new vaccine Phase I and III trials, respectively.	
Moran et al. 2007	SME-led vaccine clinical development for Malaria comprised 13% of all clinical projects in 2006. Again in 2006, SMEs had a 10% share of the global development portfolio for malaria drugs.	In comparison to observations made in 1995, malaria clinical projects were undertaken only by PPPs, public institutions and multinational companies. In 2006, multinational companies had 19% share of the global development portfolio for malaria drugs.	In 2006, the remainder of the vaccine clinical development efforts for Malaria were led by public-private partnerships (PPPs) and public institutions, accounting for 25% and 62%, respectively. In 2006, the remainder of the global development portfolio for malaria drugs

			was done by product development partnerships (47%) and public institutions (24%).
Hay et al. 2014	The study examined the success rates in clinical development of 4,451 investigational drugs in the U.S. belonging to 835 companies and involving 5,820 phase transitions during the period of 2003 to 2011. It was observed that 11% of the drug developers were small to mid-sized pharmaceutical companies or biotechnology companies developing 16% of these drugs and 85% of the drug developers were emerging biotechnology companies developing 37% of these drugs.	In contrast, 4% of the drug developers were large pharmaceutical companies or biotechnology companies developing 47% of the investigational drugs.	
Geilinger and Leo 2019	In 2018, 49% of U.S. drug approvals were owned or being licensed by smaller companies with sales amounting to $100 million or less.	In comparison, the 10 pharmaceutical companies generating the topmost sales worldwide only have a 25% share of U.S. drug approvals.	
Munos 2009	The study examined the origins of 1,222 FDA-approved new molecular entities (NMEs) between 1950 to 2008. He found, among others that: (i) 193 of these NMEs were developed by 103 small companies that were subsequently merged or acquired and thus, no longer exists; (ii) 25 were developed by 19 already-liquidated small companies; (iii) 79 were	Large companies were responsible for a decreasing share of FDA-approved NMEs, from 75% in the 1980s to 35% in 2008. With respect to projects in the discovery stage during the period from 1980 to 2004, large companies accounted for 38% of these projects.	

	developed by 23 small companies that were active from 1950 to 2008; and (iv) 105 were developed by 66 small companies that existed by virtue of merger or acquisition agreements. It was further observed that small companies were responsible for an increasing share of U.S. FDA-approved NMEs, from just approximately 23% in the 1980s to almost 70% in 2008. It was observed that, beginning 2004, "small companies have consistently matched or outperformed their larger competitors." With respect to projects in the discovery stage during the period from 1980 to 2004, small companies accounted for 47% of these projects. However, small and large companies were noted to have almost an equal share of projects in the development stage for the same period.		
Thomas 2019	In 2019, ETCs, on their own or with partners, were said to be responsible for 73% (5,067 out of 6,984) of the total global "industry" drug clinical-stage projects, with the remainder done by large companies. Disaggregated, ETCs would account for 71%, 76%, 68% and 62%	In 2019, large companies were said to be responsible for 27% of the total global "industry" drug clinical-stage projects – specifically 29%, 24%, 32% and 38% of Phase I, II, III and new drug applications, respectively.	

	of Phase I, II, III and new drug applications, respectively, as compared to those done by large companies.		
IQVIA 2019b	In 2018, it was identified that there are 74 small companies that have combined global sales of $159 billion and 446 drugs in their R&D pipeline, 9 mid-sized companies with $50 billion sales and 181 products, and 3,212 emerging biopharma companies with $139 billion sales and 8,752 products. In 2003, there were 1,383 products identified globally in the late-stage phase and this number increased to 2,891 in 2018. Comparing these data from 2003 to 2018, EBCs were observed to have an increasing share of early (from discovery until Phase I stages) and late-stage (from Phase II until registration stages) product pipelines from 68% to 84% and 52% to 73%, respectively. During the same period, small and mid-sized companies were observed to have a limited and decreasing share of late-stage product pipeline of 6% to 5% and 5% to 3%, respectively.	In 2018, 25 large companies had combined annual sales of $637 billion and 1,845 products. During the period of 2003 to 2018, the large companies exhibited a decreasing trend for late-stage product pipeline from 36% to only 19%.	
IQVIA 2019a	For 59 “new active substances” submitted for approval with the U.S. FDA	25% of these 59 substances came from large companies.	

	in 2018, it was observed that 64% of these were invented by EBCs and another 5% each by small and mid-sized companies. For the submission of these 59 substances with the FDA, 47% were done by EBCs, while 5% and 3% of these submissions were made by mid-sized and small companies respectively	Large companies were responsible for 44% of the FDA submissions with respect to these 59 substances.	

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Abstract:
Background
Antibiotic innovation has dwindled to dangerously low levels in the past 30 years. Since resistance continues to evolve, this innovation deficit can have perilous consequences on patients. A number of new incentives have been suggested to stimulate greater antibacterial drug innovation. To design effective solutions, a greater understanding is needed of actual antibiotic discovery and development costs and timelines. Small and medium-sized enterprises (SMEs) undertake most discovery and early phase development for antibiotics and other drugs. This paper attempts to gather a better understanding of SMEs' targets, costs, and durations related to discovery and early phase development of antibacterial therapies.

Methods
DRIVE-AB, a project focused on developing new economic incentives to stimulate antibacterial innovation, held a European stakeholder meeting in February 2015. All SMEs invited to this meeting ($n = 44$) were subsequently sent a survey to gather more data regarding their areas of activity, completed and expected development costs and timelines, and business models.

Results
Twenty-five companies responded to the survey. Respondents were primarily small companies each focusing on developing 1 to 3 new antibiotics, focused on pathogens of public health importance. Most have not yet completed any clinical trials. They have reported ranges of discovery and development out-of-pocket costs that appear to be less expensive than other studies of general pharmaceutical research and development (R&D) costs. The duration ranges reported for completing each phase of R&D are highly variable when compared to previously published general pharmaceutical innovation average durations. However, our sample population is small and may not be fully representative of all relevant antibiotic SMEs.

Conclusions
The data collected by this study provide important insights and estimates about R&D in European SMEs focusing on antibiotics, which can be combined with other data to design incentives to stimulate antibacterial innovation. The variation implies that costs and durations are difficult to generalize due to the unique characteristics of each antibiotic project and depend on individual business strategies and circumstances.

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Abstract: The costs of developing the types of new drugs that have been pursued by traditional pharmaceutical firms have been estimated in a number of studies. However, similar analyses have not been published on the costs of developing the types of molecules on which biotech firms have focused. This study represents a first attempt to get a sense for the magnitude of the R&D costs associated with the discovery and development of new therapeutic biopharmaceuticals (specifically, recombinant proteins and monoclonal antibodies [mAbs]).

We utilize drug-specific data on cash outlays, development times, and success in obtaining regulatory marketing approval to estimate the average pre-tax R&D resource cost for biopharmaceuticals up to the point of initial US marketing approval (in year 2005 dollars). We found average out-of-pocket (cash outlay) cost estimates per approved biopharmaceutical of $198 million, $361 million, and $559 million for the preclinical period, the clinical period, and in total, respectively. Including the time costs associated with biopharmaceutical R&D, we found average capitalized cost estimates per approved biopharmaceutical of $615 million, $626 million, and $1241 million for the preclinical period, the clinical period, and in total, respectively. Adjusting previously published estimates of R&D costs for traditional pharmaceutical firms by using past growth rates for pharmaceutical company costs to correspond to the more recent period to which our biopharmaceutical data apply, we found that total out-of-pocket cost per approved biopharmaceutical was somewhat lower than for the pharmaceutical company data ($559 million vs $672 million). However, estimated total capitalized cost per approved new molecule was nearly the same for biopharmaceuticals as for the adjusted pharmaceutical company data ($1241 million versus $1318 million). The results should be viewed with some caution for now given a limited number of biopharmaceutical molecules with data on cash outlays, different therapeutic class distributions for biopharmaceuticals and for pharmaceutical company drugs, and uncertainty about whether recent growth rates in pharmaceutical company costs are different from immediate past growth rates.

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Abstract: Starting biotech or pharmaceutical companies is traditionally thought to be based around a scientist, their technology platform or a clinical candidate spun out from another company. Between us we have taken a different approach and formed two small early stage companies after initially leveraging the

perspective of a parent with a child with a life-threatening rare disease. Phoenix Nest (http://www.phoenixnestbiotech.com/) was co-founded to work on treatments for Sanfilippo syndrome a devastating neurodegenerative lysosomal storage disorder. In the space of just over 3 years we have built up collaborations with leading scientists in academia and industry and been awarded multiple NIH small business grants. The second company, Collaborations Pharmaceuticals Inc. (http://www.collaborationspharma.com/) was founded to address some of the other 7000 or so rare diseases as well as neglected infectious diseases. The Rare Pediatric Disease Priority Review Voucher is likely the most important incentive for companies working on rare diseases with very small populations. This may also be partially responsible for the recent acquisitions of rare disease companies with late stage candidates. Lessons learned in the process of starting our companies are that rare disease parents or patients can readily partner with a scientist and fund research through NIH grants rather than venture capital or angel investors initially. This process may be slow so patience and perseverance is key. We would encourage other pharmaceutical scientists to meet rare disease parents, patients or advocates and work with them to further the science on their diseases and create a source of future drugs.
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Abstract: A successful new product development strategy involves the identification, development, and exploitation of key resources. Such exploitation of a firm's unique knowledge base ultimately leads to successful new products and, in turn, a sustainable competitive advantage. In this paper, we look at a firm's knowledge strategy along three dimensions, and examine the impact of firm size and age on the type of knowledge strategies used to build technological strength and competitive success. The three dimensions of knowledge strategy examined are: extent of emphasis on speed of learning, emphasis on internal versus external sourcing of knowledge, and the development of a broad versus a narrow knowledge base. Using a population of 27 firms from the drug delivery sector of the pharmaceutical industry, we found that firm size and age influenced the success of firm knowledge strategies. Interestingly, we found that the differences in the knowledge strategy dimensions between large and small firms and between old and young firms were not as great as expected. However, we found that firm size and age moderate the relationship between knowledge strategies and technological strength. In other words, firms that used appropriate knowledge strategies for their size and age optimized their technological strength. Concerning size, smaller firms that focused on faster learning and developing a narrow knowledge base were able to optimize technological strength. On the other hand, large firms that developed a broader knowledge base and focused on internal learning achieved similar success. Concerning age, younger firms that maintained connections to external sources of learning and developed a

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Abstract: Advanced therapy medicinal products (ATMPs) hold promise as treatments for previously untreatable and high-burden diseases. Expectations are high and active company pipelines are observed, yet only 10 market authorizations were approved in Europe. Our aim was to identify challenges experienced in European ATMP clinical development by companies. A survey-based cohort study was conducted among commercial ATMP developers. Respondents shared challenges experienced during various development phases, as well as developer and product characteristics. Descriptions of challenges were grouped in domains (clinical, financial, human resource management, regulatory, scientific, technical, other) and further categorized using thematic content analysis. A descriptive analysis was performed. We invited 271 commercial ATMP developers, of which 68 responded providing 243 challenges. Of products in development, 72% were in early clinical development and 40% were gene therapies. Most developers were small- or medium-sized enterprises (65%). The most often mentioned challenges were related to country-specific requirements (16%), manufacturing (15%), and clinical trial design (8%). The European ATMP field is still in its early stages, and developers experience challenges on many levels. Challenges are multifactorial and a mix of ATMP-specific and generic development aspects, such as new and orphan indications, novel technologies, and inexperience, adding complexity to development efforts.

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Abstract: Many serious diseases lack safe and effective vaccines. Using a large commercial database, we examined trends in global vaccine research and development and found that the proportion of new vaccine candidates entering all stages of clinical development increased by 3-5 percentage points over the past two decades. Small and medium-size companies accounted for nearly twice as many new Phase I vaccine trials compared to large companies, but late-stage (Phase III) vaccine trials were dominated by large companies. There were no significant differences between vaccines and drugs in the probability of success in clinical trials or in profitability. Small and medium-size companies, including spin-outs from academic research centers, play an important role in innovative research and discovery. Our findings suggest that policy making targeted at smaller companies, such as prizes or opportunities for public-private partnerships, could support the development of new vaccines, particularly those targeting unmet medical needs and emerging public health threats.

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Abstract: Forged in the early 1960s, the paradigm for pharmaceutical innovation has remained virtually unchanged for nearly 50 years. During a period when most other research-based industries have made frequent and often sweeping modifications to their R&D processes, the pharmaceutical sector continues to utilize a drug development process that is slow, inefficient, risky, and expensive. Few who work in or follow the activities of the pharmaceutical industry question whether change is coming. They know that the pharmaceutical sector, as currently structured, is unable to deliver enough new products to market to generate revenues sufficient to sustain its own growth. Nearly all major drug developers are critically examining current R&D practices and, in some cases, considering a radical overhaul of their R&D models. But key questions remain. What will the landscape for pharmaceutical innovation look like in the future? And, who will develop tomorrow's medicines?

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Abstract: Understanding the factors that promote drug innovation is important both for improvements in health care and for the future of organizations engaged in drug discovery research and development. By identifying the inventors of 252 new drugs approved by the US Food and Drug Administration from 1998 to 2007 and their places of work, and also classifying these drugs according to innovativeness, this study investigates the contribution of different types of organizations and regions to drug innovation during this period. The data indicate that drugs initially discovered in biotechnology companies or universities accounted for approximately half of the scientifically innovative drugs approved, as well as half of those that responded to unmet medical needs, although their contribution to the total number of new drugs was proportionately lower. The biotechnology companies were located mainly in the United States. This article presents a comprehensive analysis of these data and discusses potential contributing factors to the trends observed, with the aim of aiding efforts to promote drug innovation.

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Abstract: A clear vision for vaccines research and development (R&D) is needed if Europe is to continue to lead the discovery of next generation vaccines. Innovation Partnership for a Roadmap on Vaccines in Europe (IPROVE) is a collaboration between leading vaccine experts to develop a roadmap setting out how Europe can best invest in the science and technology essential for vaccines innovation. This FP7 project, started in December 2013, brought together more than 130 key public and private stakeholders from academia, public health institutes, regulators, industry and small and medium-sized enterprises to determine and prioritise the gaps and challenges to be addressed to bolster innovation in vaccines and vaccination in Europe. The IPROVE consultation process was structured around seven themes: vaccine R&D, manufacturing and quality control, infrastructure, therapeutic vaccines, needs of small and medium-sized enterprises, vaccines acceptance and training needs. More than 80 recommendations were made by the consultation groups, mainly focused on the need for a multidisciplinary research approach to stimulate innovation, accelerated translation of scientific knowledge into technological innovation, and fostering of real collaboration within the European vaccine ecosystem. The consultation also reinforced the fact that vaccines are only as good as their vaccine implementation programmes, and that more must be done to understand and address vaccination hesitancy of

both the general public and healthcare professionals. Bringing together a wide range of stakeholders to work on the IPROVE roadmap has increased mutual understanding of their different perspectives, needs and priorities. IPROVE is a first attempt to develop such a comprehensive view of the vaccine sector. This prioritisation effort, aims to help policy-makers and funders identify those vaccine-related areas and technologies where key investment is needed for short and medium-long term success.

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Abstract: Despite unprecedented investment in pharmaceutical research and development (R&D), the number of new drugs approved by the US Food and Drug Administration (FDA) remains low. To help understand this conundrum, this article investigates the record of pharmaceutical innovation by analysing data on the companies that introduced the ~1,200 new drugs that have been approved by the FDA since 1950. This analysis shows that the new-drug output from pharmaceutical companies in this period has essentially been constant, and remains so despite the attempts to increase it. This suggests that, contrary to common perception, the new-drug output is not depressed, but may simply reflect the limitations of the current R&D model. The implications of these findings and options to achieve sustainability for the pharmaceutical industry are discussed.

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Abstract: Global healthcare innovation networks nowadays have expanded beyond developed countries with many developing countries joining the force and becoming important players. China, in particular, has seen a significant increase in the number of innovative firms and research organizations stepping up to the global network in recent years. Nevertheless, the intense Research and Development input has not brought about the expectable output. While China is ascending at a great speed to a leading position worldwide in terms of Research and Development investment, scientific publications and patents, the innovation capabilities in the pharmaceutical sector remain weak.

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Abstract: SME's are integral pillars in ladder of innovation. Due to their proximity to end users and their flexibility, they are credited with the creation of ground level product and process innovations in their local and world markets. SMEs absorption of innovations is significantly assisted by the entrepreneurial environment, globalization tendencies, rapidly changing technological issues of the environment as well as other determinants. However, depending on the industry, determinants of innovation affects each firm differently depending on the type of innovation considered. The goal of this research is therefore, to analyse what determinants influence the innovation activities of small and medium enterprises across three different German industries, namely, in the Electrical, Chemical and Pharmaceutical and the Metal Industry. Results from

the SMEs were compared against themselves as well as SMEs from the three considered industries. This paper used data from the Community Innovation Survey (2010-2012) which employed stratified sampling technique with surveys. Logistic regression tool was used to analyse the impact of certain activities and expenditures, information and competitive strategies on product on process innovation. The research eventually discovered that the determinants influencing product and process innovations in selected enterprises varied according to the size of enterprise analysed. It was proposed that small enterprises should primarily focus on In-house R&D and acquisition of capital assets whilst medium size enterprises would be best served in concentrating on training for innovative activities.
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Abstract: Recent developments in vaccine research provide new momentum for an important area in health innovation. Particularly interesting are novel DNA vaccine approaches, many of which are already under clinical investigation. The Framework Programmes of the European Union play an important role in supporting collaborative efforts in vaccine research to develop new and better vaccines and bring them to the market. With a timely strategic reorientation towards a sustainable investment in innovation, the current seventh Framework Programme will help to bring large industry and small and medium-sized enterprises (SME) on board and foster partnership between stakeholders. As the first human DNA vaccines progresses through the development pipeline, more and more questions revolve around licensing and regulation and appropriate guidelines are being developed.

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Abstract: The paper aims to show how licensing behaviour can be used to differentiate distinct innovation

strategies. Information on in-licensing and out-licensing agreements is used to guide the development of a framework that details the licensing firm's relational preference for internal and external orientation. Using firm-level data of the Korean pharmaceutical firms, the study categorised the distinct strategic orientations of firms based on the proposed matrix model. The results indicated that firms with higher R&D (research and development) expenditures have a tendency to greater external exploitation of technological knowledge than firms with low R&D spending. The study provides potential avenues for targeting of licensing partners from the perspective of firms seeking to in-license or out-license their innovations.

Link:https://www.tandfonline.com/doi/pdf/10.1080/09537325.2018.1490711?needAccess=true

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Abstract: Not available

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Abstract: The purpose of this paper is to discuss how small and middle-sized enterprises (SMEs) utilize open innovation in practice. Open innovation has become a well-used rhetorical concept among key bio-pharmaceutical spokespersons, suggesting that it would help to renew the stagnated industry. We report a survey (N = 104) on Swedish SMEs in the bio-pharmaceutical industry, where we shed light on how widespread the knowledge and practical uses of open innovation activities actually are. The findings not only show that very few respondents are aware of the open innovation concept, but also that open innovation-related activities are to a large extent integrated within their ordinary innovation practices. The study also suggests that firms that are engaged in open innovation activities tend to be more innovation-productive than those who do not. Based on these findings, we propose that there is a casual relation between open innovation and entrepreneurial growth, in which open innovation activities can act as accelerators for entrepreneurial growth. At the same time, much 'openness' is still performed on informal and ad-hoc basis by SMEs in the industry.

L'objectif de cet article est d'examiner la manière dont les petites et moyennes entreprises (PME) ont recours à l'innovation partagée en pratique. L'innovation partagée est devenue un concept rhétorique chez les porte-paroles clés de la biopharmacie, ce qui laisse entendre qu'elle pourrait revitaliser cette industrie stagnante. Nous rendons compte d'une enquête (n = 104) sur les PME suédoises engagées dans l'industrie biopharmaceutique, sur laquelle nous apportons un éclairage en ce qui concerne l'ampleur réelle des connaissances sur les activités d'innovation partagée et leur utilisation pratique. Les résultats montrent que très peu de répondants savent l'existence du concept d'innovation partagée, mais également que les activités qui sont en lien avec elle tendent à être plus productives, en termes d'innovation, que celles qui ne le sont pas.

Sur foi de ces résultats, nous émettons l'hypothèse qu'il existe un rapport informel entre l'innovation partagée et la croissance entrepreneuriale, en ce sens que les activités de la première peuvent jouer un rôle d'accélérateur de la seconde. Dans le même temps, beaucoup de « partage » est encore réalisé sur une base informelle et ad hoc par les PME dans cette industrie.

Link : https://www.tandfonline.com/doi/full/10.1080/08276331.2016.1145502

** For the purposes of this review, we have established three categories to describe the state of the literature: thin, considerable, and rich.*

- *Thin: There are relatively few papers and/or there are not many recent papers and/or there are clear gaps*
- *Considerable: There are several papers and/or there are a handful of recent papers and/or there are some clear gaps*
- *Rich: There is a wealth of papers on the topic and/or papers continue to be published that address this issue area and/or there are less obvious gaps*

Scope: While many of these issues can touch a variety of sectors, this review focuses on medicines. The term medicines is used to cover the category of health technologies, including drugs, biologics (including vaccines), and diagnostic devices.

Disclaimer: The research syntheses aim to provide a concise, comprehensive overview of the current state of research on a specific topic. They seek to cover the main studies in the academic and grey literature, but are not systematic reviews capturing all published studies on a topic. As with any research synthesis, they also reflect the judgments of the researchers. The length and detail vary by topic. Each synthesis will undergo open peer review, and be updated periodically based on feedback received on important missing studies and/or new research. Selected topics focus on national and international-level policies, while recognizing that other determinants of access operate at sub-national level. Work is ongoing on additional topics. We welcome suggestions on the current syntheses and/or on new topics to cover.