COMPLEXITY, ROUTINES, AND SUSTAINABILITY OF PHARMACEUTICAL INNOVATION

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ABSTRACT

This paper examines how the routines for drug discovery and development that were built up by leading U.S. pharmaceutical firms in the twentieth century translate into a sustainable advantage. Due to the complexity of pharmaceutical R&D that is associated with high risk, a capability to guide R&D activity in the direction of reducing the risk is important. History shows that the leading firms have enjoyed the longevity and high profitability for a long time. How has this been possible? Do routines facilitate innovation? This study finds that the availability of routine procedures for detecting early signs of success in drug discovery and reproducing past discoveries facilitates R&D activity. Furthermore, using the past partial solutions (e.g., molecules that showed some desirable activity in the past) as building blocks in search of a new drug, pharmaceutical firms could have reduced high risk inherent in pharmaceutical innovation.

KEYWORDS

Complexity; Routines; Sustainability

1. Introduction

This paper examines sustainability of innovation by focusing on complexity in carrying out pharmaceutical innovation. Today, drug discovery and development follow a well-defined routine procedure. The history of the U.S. pharmaceutical industry suggests that this type of routinized R&D became first visible in the 1940s and 1950s. Since then, leading innovators have enjoyed high profitability until recently. This implies that innovators may have been able to develop capabilities to reduce high risk inherent in R&D activity and sustain it.

The objective of this paper is to unravel the sustainability of R&D. It is argued that if chance is only a determinant

for success in dealing with such high risk, we should not have observed the recurring pattern of innovation in the U.S. pharmaceutical industry. In particular, we pay attention to the two nonrandom factors in the drug discovery routine that facilitates innovation. First, we exemplify how the availability of routine procedures for reproducing past discoveries and detecting early signs of success in drug discovery facilitates R&D activity. Second, search processes using past discoveries and knowledge as building blocks are identified as a key factor that reduces a high risk in drug innovation.

2. Search Routines and Complexity

Today leading pharmaceutical companies routinely identify, modify and screen many thousands of compounds. Among those, only a few that pass the desired levels of efficacy and safety become candidates for clinical testing. Innovation activity of this kind is built into some routine procedures.

In these procedures, the screening of potential candidates involves decision-making with enormous choice variables. Decision making of this sort is very complex not only because of the sheer number of variables drug firms should consider but also of combinatorics in many one-at-a time modifications. In particular, the presence of drug interactions creates an unexpected problem. When two or more incompatible chemicals are combined, they can produce an unexpected, disastrous reaction to the body. Perhaps, the drug interactions may not be too pervasive to the extent that everything interacts with everything else. Yet, because of the lack of systematic studies of drug interactions in the medical literature, there is little guidance for drug firms to follow in avoiding hazardous interactions[1].

In the literature on complexity, surged interest is on these kinds of interactions, which make the search problem particularly difficult[2, 3, 4, 5, 6]. In the case of pharmaceuticals, the presence of drug interactions basically says that the therapeutic effect of the synthesized drug would not be known ex ante even when a drug firm completely knows about the behavior of each ingredient separately. If a firm knows how drug interactions work, it can reduce the scope of search to a reasonably degree. Unfortunately, this is not usually the case. To discover the best-performing molecule, the firm, then, has to check every conceivable combination of substances because each combination potentially has a different therapeutic effect. Indeed, the search space for drug discovery and development has been known to be immense.

In dealing with such immense possibilities, exhaustive search is practically impossible. That is, firms have to sample the space in search of new potent and safe drugs. Apparently, market selection could easily go against firms that regularly carry out drug discovery and development if chance is only a determinant for success. Here the recurrence of drug discovery and development in these firms hinges on whether they can safeguard their positions not only from

competitive erosion, but also from hostile nature inherent in the combinatorics. Not surprisingly, drug companies in most countries have not shown vitality of pharmaceutical innovation. On the other hand, top pharmaceutical companies in the U.S. have been claimed to have the ability to survive costly failure in drug discovery and development [7, 8].

How, then, have these pharma giants been able to tame these wild combinatorics? Would there be factors in routines that facilitate innovation? In general, routinization means that choice is simplified by the development of some fixed response to defined stimuli[9]. In the space of immense possibilities, the advantages of programmed choice of this sort can be attained by reducing option selection to well-defined channels, thereby speeding up the decision making process[9]. However, the question is whether this programmed choice or programmed sampling is more likely to lead firms to a path toward success than failure.

3. ROUTINES FACILITATE INNOVATION

This paper addresses the above question by focusing on two characteristics of routines: (1) reproducibility and (2) building block search. The first, well-known, feature of routines is reproducibility or memory[10, 11, 12]. First, consider reproducibility. One aspect of reproducibility is associated with accurate and reliable measurement of biological activity under any circumstances. For example, biologicals are perishable and easily contaminated. Slippage of rigid reproducibility of a once-discovered therapeutic agent could mean a loss of its therapeutic effect or sometimes a catastrophe. An outbreak of tetanus in Camden, New Jersey in 1901 was alleged to be connected to contaminated smallpox vaccine[13]. Fueled by this incident, the Biologicals Control Act, one of the first modern drug regulations in the United States, was passed in 1902 to regulate production and sale of biologicals.

Accurate, reliable measurement matters not only in production but also in R&D. Nelson[14] emphasized the importance of the availability of cheap and reliable tests in guiding R&D activity. Drug discovery and development require the cumulative selection over a long sequence of the multi-step trials and errors. In particular, costs increase dramatically with the later stages of drug development. Today, on average, about one third of R&D expenditure is spent on clinical trials. To reduce costly failure at the last stage, a firm should be able to come up with a few optimal candidates with desired activity beforehand. The more slippage in testing routines there is at the early stages, the more candidates with less desirable attributes will enter into the later stages of drug discovery and development, and the more costly the failure will be. Thus, without some rigid ways of detecting and testing desired activity of each compound early on, it may be a good idea for the firm not to even start a search or to focus on the area where rigid testing routines are readily available.

In the absence of such rigid testing procedures, it is not surprising that the pre-innovative era was characterized by a myriad of inadequate trials and errors in the war against diseases. Inadequate trials and errors had been found in mold therapy before Flemining뭘 discovery. The ancient Chinese and Indians used a crude form of this approach to cure some infections[15]. It is also claimed that the Mayans used a fungus for the treatment of ulcers and intestinal infections[16]. Also, fossil evidence for traces for tetracycline was found in the remains of a tribe who lived in Sudanese Nubia around 350 AD[17]. However, such crude therapy in the pre-antibiotic era was linked neither to understanding of complex, bacterial infections nor to development of efficacious antibiotics.

The development of the first efficacious antibiotic took a long journey. Since Mosses suggested a therapeutic value of a microbe in a letter to *Lancet* in 1852[16], numerous scientific attempts had existed with some occasions of near misses before Fleming뭘discovery in 1928[18]. Even Fleming뭘discovery did not directly result in the development of an efficacious cure, since the crude penicillin he found showed instability in its therapeutic effect[17]. Purifying and preserving it in a stable form requires another very rigid precision based on mastery of complex chemistry. However, Fleming뭘discovery is distinct from the numerous, previous trials and errors, because this event opened the door to development of a useful drug. When the locus of action was moved to Florey and his Oxford group, their 뱋nterest in germ killers led both *to Fleming's paper and to a supply of his penicillin culture*□ 18, p. 48]. Here, it is important from the evolutionary viewpoint that Fleming뭘invaluable luck was not wasted in vain, and that the Oxford group did not have to reinvent the wheel from scratch thanks to preservation of his crude penicillin.

The story above suggests that complex therapeutic agents like penicillin can be assembled through a series of chance events. If any single part of these trials fails, there will be no solution in the war against disease-causing agents. When ready-made discoveries cannot be reproduced over time, these chance events should jointly happen in one shot to be of any use. Furthermore, evolution has to recreate them again and again in the future. If these possibilities are small, it may not reappear again and again. In sum, without such rigid reproducibility, evolution loses its continuity.

Now, let us explore the second major aspect of routine, building block search. We claim that there is a striking parallel between development of new drugs and writing new computer programs. When one writes a new program, he or she does not start from scratch. There are numerous ready-made subroutines or libraries, which have proven records for their performance. Then, the programmer뭘job is in part to use these proven routines and subroutines as building blocks to create new programs. The more diverse bug-free routines there are, the easier the programmer can create a new program. If this analogy applies to invention and innovation, there is some hope for explaining how leading pharmaceutical firms have reduced risks of R&D, thereby constantly dashing to uncertain territories of innovation.

As is the case in programming, drug firms usually do not start from scratch when they develop a new drug. As mentioned before, the Oxford group did not start from any random point on the space of immense possibilities, but built upon the Fleming뭲 crude penicillin, a partial solution to problems of bacterial infection. In reality, drug firms maintain production routines, or knowledge to reproduce existing drugs, and build some knowledge base about how these drugs act in human body. Furthermore, large pharmaceutical firms accumulated extensive decades-old collection of compounds, or what is called 뱧ibrary.□ On the space of immense possibilities, this existing knowledge basis can be a logical place to start searching for new drugs.

Drug search in the early twentieth century was indeed carried out through molecular modification by using known compounds as building blocks[18]. The original salvarsan was discovered after many, many trials and failures. Ehrilic called it □ 06□ because it was the 606th combination tried[15]. This original salvarsan had an undesirable side effect. Given the availability and the rigid preservation of this molecule, improving it is not as hard as discovering it. A researcher can modify some elements of it to see if this trial can improve upon the original quality. If not, he or she can discard it and try another attempt. In this way, neosalvarsan, a less toxic combination that replaced the original in therapy, was discovered in the 914th arsenical test.

Similarly, Domagk뭲 discovery of prontosil triggered a dominant paradigm in the 1930s and 1940s: innovation was attempted based on building blocks of sulfanilamide, an active ingredient of prontosil[19]. These activities led to the identification of 뱧ell over 10,000 sulfanilamide derivatives□ for the treatment of both infectious and non-infectious diseases[18, p. 45].

Firm capability in reducing risk from drug discovery stems primarily from reducing the role of chance on the space of immense possibilities. That is, chance for success depends on where the search starts from, or whether there exist many ready-made partial solutions, or building blocks for innovation. Indeed, success in drug discovery had been largely correlated with the size of a firm뭲 library of molecules[7]. In this context, firm뭲 idiosyncratic dynamic capability lies in what kinds of molecules constitute the firm뭲 chemical library, which is a collection of past search efforts and, at the same time, a starting point for future search.

4. DISCUSSION AND CONCLUSION

We have examined routine drug discovery and development. Partly due to the complexity of diseases and partly due to unavailability of routines to detect early signs of success in drug discovery and to capture useful discoveries of the

past, development of new drugs had been dormant for a long time. Those firms that foresaw rigid scientific tools as a vehicle of moving ahead of competition routinized the search for new drugs and changed the nature of competition.

The search space for drug discovery and development is known to be immense, and to date, the pharmaceutical industry has barely scratched the surface of it[20]. Therefore, it will be a daunting task if anyone attempts to develop a cure by randomly walking through this vast space step by step. In such an attempt, chance plays a dominant role. Path-breaking research carried out by exceptional individuals (e.g., Ehrlich's discovery or Fleming's discovery) appears to be like this. In this paper, we have argued that firms cannot routinize their search activity only relying on chance event of this sort, for the chance is too small to recover their regular investment costs. There should have been some factors that make innovations more regular. Our study suggests that the embedded rule into routinized search for drug discovery and development was building block search, which in studies of genetic algorithms, is the key to tame the wild combinatorics in the space of immense possibilities.

Recently, a stream of research has begun to pay attention to dynamic capabilities[21]. It has been argued that the conventional strategy research has been relatively silent about strategies in dealing with nature by focusing large attention on winning strategies against competitors. Historical analysis of the pharmaceutical industry in this paper is suggestive of the existence of dynamic capabilities, which are supposed to safeguard firms not only against competitive erosion but also against hostile nature inherent in innovation.

Like other historical science studies, this study has a fundamental limitation. The story told here is primarily a reconstruction of the past in light of evolutionary theory. Thus, it says nothing about whether this story generalizes beyond the context considered here. From the illustrative evidence in the "glory" of historical detail, we can only obtain some glimpse of underlying mechanisms behind evolution of complex systems. The present work can be considered a crude beginning to examine how routines facilitate innovation. Further studies of these sorts are needed in diverse historical contexts to develop a systematic body of knowledge.

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