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Innovation vs Financialization: an Analysis on the United States as a Source of Innovation for European Big Pharma

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SUMMARY

Driven by the perspective of maximizing shareholder value (MSV), the U.S. biopharmaceutical industry has adopted a highly financialized business model. In such a model, the key metrics are stock-price performance, earnings per share, and dividend yield, supported by distributions to shareholders in the forms of dividends and stock buybacks. Such value extraction is incentivized by stock-based executive pay and can be pursued at the expense of productivity in drug innovation (Lazonick et al. 2017). Yet with government support for drug development through the National Institutes of Health and various forms of intellectual property protection and government financial subsidies as well as unregulated drug prices that can provide high profits for reinvestment in drug development, the U.S. prescription drug market should be highly conducive to innovation in drug development (Lazonick and Tulum 2011). This paper asks whether less-financialized European pharma companies, which are subject to price regulation in their home markets, can make use of U.S. business conditions to engage in innovation by tapping into the immense knowledge base in the United States and selling their products in the United States at high, unregulated, prices. Making use of Lazonick's social conditions of innovative enterprise framework, the analytical approach employed in this research inquiry is twofold. First, the sources of innovative capabilities within the top seven European pharma companies are examined. Second, for the purpose of this particular paper, the top innovation performer among the seven companies is identified for a firm-level case analysis to explore how a non-financialized company can make better use than financialized companies of capabilities and incentives available in the US drug market to achieve greater productivity. As the top performers in the US drug market, Novartis, Hoffmann-La Roche, GlaxoSmithKline, AstraZeneca, Bayer, Merck KGaA, and Sanofi-Aventis are selected for product analysis. The analysis reveals the geographic origins of pharma products and geographic sources of pharma revenues of these European companies. Identified as the top performer by various different productivity attributes, the case-analysis of Swiss-based Roche (Hoffman-La Roche) explains how a non-financialized outsider to a national economy can gain competitive advantage by operating in that economy in ways that financialized insiders, undermined by MSV, cannot.

INTRODUCTION

The U.S. biopharmaceutical (BP) industry, made up of "old economy" Big Pharma companies and "new economy" biopharma companies, has become a highly financialized business model in which, in the name of maximizing shareholder value, stock-price performance has become of paramount importance. The clearest manifestations of financialization are massive distributions to shareholders in the forms of dividends and stock buybacks, incentivized by exploding stock-based executive pay (Lazonick et al. 2017).

Control over firms within the industry is increasingly dominated by financial interests who are more interested in extracting the gains from past innovation than in mobilizing labor and capital to generate new innovation. Moreover, hundreds of younger biopharma firms that are listed on the stock market are what Lazonick, Sakinç, and Tulum have called "product-less IPOs, or PLIPOs, in which through speculation in and manipulation of the firm's stock price, financial interests can reap tens, or even hundreds, of millions of dollars, even without a commercial product (Lazonick and Sakinç, 2010; Lazonick and Tulum, 2011; Sakinç and Tulum 2012; Lazonick et al. 2017).

The extent of these distributions to shareholders has been supported by the willingness of the U.S. government to forgo the regulation of prescription-drug prices, making the United States unique among advanced nations. Data collected by the UK Pharmaceutical Price Regulation Scheme for 2004 through 2010 shows that US prices were about two and a half times those of most other advanced economies, and that the disparity was increasing over time.

With the UK price index at 100 in 2010, the US index was 254, while the French index was 95, the Italian 103, and the German 142 (UK Department of Health 2012, p. 30). For decades, US pharma has argued that high drug prices enable its companies to augment investment in drug R&D and accelerate drug innovation. But the evidence shows that, far from providing enhanced funding for value creation, since the mid-1980s US pharma companies have used high drug prices to financed distributions to shareholders.

Meanwhile the US government provides pharma with knowledge bases, productive capabilities, financial subsidies, tax breaks, and intellectual-property protections, all meant to support drug innovation. From 1938 through 2016, the US National Institutes of Health (NIH) expended $1 trillion, measured in 2016 dollars, funding life sciences research. The 2016 NIH budget was $32.2 billion (NIH). The US system of higher education produces a world-leading STEM (science, technology, engineering, mathematics) labor force available to US pharma and biopharma firms. More generally US governments at the national, state, and local levels provide financial subsidies and tax breaks to firms in the pharmaceutical industry.

In 1980, the Bayh-Dole Act explicitly permitted research institutes, most of them housed at universities, to transfer the results of federally funded research to commercial entities. In 1983 the US government passed the Orphan Drug Act that provides financial subsidies and market protection to companies to support innovation in drugs for rare and genetic diseases—drugs that, as Lazonick and Tulum (2011) have shown, were the foundation for biopharma revenue growth in the 1990s and 2000.

In 1995, the US government extended patent protection from 17 to 20 years, a benefit demanded by and of immense importance to the pharmaceutical industry. And the US prescription drug market is enormous; in 2015 it amounted to US$324.5bn., representing over 10 percent of national health expenditures (CMS 2015).

While our research has shown that the major US pharma and biopharma companies are highly financialized, these characteristics of the US pharmaceutical drug industry provide an ideal environment for a non-financialized company that is willing to reinvest its profits in drug development to generate innovation. Such should be especially the case for European pharma companies that are subject to price regulation in their home markets if they can tap the immense knowledge base in the United States and sell their products in the United States at high, unregulated, prices.

The basic hypothesis is that, based in what are often called "social market economies", European pharma companies will be less influenced by MSV ideology and hence exposed to its destructive impacts on drug innovation. The purpose of this paper is to undertake an exploration of the operation and performance of major European pharma companies that are highly active in developing and selling drugs in the United States to gain insight into this "innovation versus financialization" hypothesis.

This paper employs Lazonick's *theory of innovative enterprise* (TIE) framework to gain insight into such hypothesis. As Lazonick (2015) explains through his TIE framework, the success in transforming productive resources into innovative goods and services is determined by the presence of the three s*ocial conditions of innovative enterprise* (SCIE): *strategic control, organizational integration* and *financial commitment.* Financialization can undermine these social conditions, impeding the productive efforts of previously innovative organizations (Lazonick 2009).

Given the human and financial resources that the United States makes available to BP firms and the competitive advantages that, historically, US BP companies have possessed in the US economy, it is important to understand whether, how and why Europe-based companies have been able outperform their US competitors in taking advantage of economic opportunities that are available to all the companies operating in the United States.

The findings in this report support the hypothesis that the possession of an innovative business model has given major European firms a competitive advantage over US firms because the US-based competitors have increasingly turned from an innovative to a financialized business model. If such is the case, it provides a strong argument to European policy-makers to recognize the destructive impacts of MSV ideology and erect barriers to its pernicious spread from the United States to Europe.

The analysis in this study focuses on Europe's most competitive companies in the global drug market that have historically had a well-established presence in the drug industry and persisted through various different restructuring periods during the evolution of this industry. Novartis and Hoffmann-La Roche from Switzerland; GlaxoSmithKline and AstraZeneca from the United Kingdom; Bayer and Merck KGaA from Germany; and Sanofi-Aventis from France are the most competitive drug companies globally that are based in Europe, and all have a long history in the industry.

The analysis conducted on the products of those seven companies revealed that in 2015 Roche was the top performer in various different dimensions among the seven companies examined. Based on the financial figures filed with the US Securities and Exchange Commission (SEC) for 2015, Roche was second after Johnson & Johnson in terms of consolidated corporate sales. However, when the comparison is made based on pharmaceutical product sales only, Roche outperformed all the global competitors.[1]

[1] The global ranking of top pharma company for 2015 was published by a pharma market intelligence company, IgeaHub, access via https://igeahub.com/2016/05/06/top-10-pharmaceutical-companies-2016/ . In this list J&J is

Roche's 2015 position represents an impressive improvement from its number 11 ranking in 1990 with US$2.9bn global sales figure in a list that was headed by US-based Merck & Co. (not to be confused with German Merck KGaA) with US$5.2 global sales. Merck & Co., the most innovative pharma company in the world in the 1980s and early 1990s, was ranked number 6 in 2015, falling behind Roche.

Roche's current global position is a result of its organizational commitment to building a competitive knowledge-base that was first initiated in the late-1960s. At that time, the company was enjoying the financial windfall that resulted from the introduction of the first pharmaceutical blockbuster, an iconic tranquilizer marketed as Valium. Recognizing the potential value of the fledging new fields of biology, biochemistry and molecular biology, Roche ploughed back such windfall generated from Valium into the acquisition of new knowledge in molecular biology.

During the biotechnology revolution of the 1980s and 1990s Roche was one of the very few big pharma companies that was strategically positioned in the forefront of an emerging science, molecular genetics that would disrupt the pharmaceutical industry. Roche had acquired and developed a competitive knowledge base in molecular genetics through its close relation with Genentech, arguably the world's first biotechnology company established in 1976.

Genentech was formed at the onset of the biotechnology revolution with the purpose of becoming an independent and fully integrated pharma company (FIPCO) by leveraging a powerful drug discovery and development tool, recombinant DNA (rDNA) technology. Genentech and Roche were among the very few companies that possessed the technological capabilities and scientific skill to utilize such a powerful tool in the innovation of new therapies. Started as a drug development partnership in the late-1970s, the relationship between Roche and Genentech would take a new turn in the late-1980s when Genentech's financial resources had depleted and sought help from Roche to push its strong pipeline of innovation therapies through clinical.

The structure of the paper as follows. In the next section the social conditions of innovation are analyzed in the context of Roche. Through a systematic case analysis of Roche this study provides insights into the ways in which innovation-led growth can be attained through the abilities and incentives of strategic managers engage in innovation for the sake of the growth of the firm.

In the final section of the paper, I analyze the events that led to Roche's acquisition Genentech and a key technology, PCR, from Cetus from the SCIE perspective. The case analysis of Roche's two key acquisitions will explain how a non-financialized outsider to a national economy can benefit from productive resources of an organization in ways that financialized insiders, undermined by MSV, cannot. Finally, through the case analysis of the first biotech PLIPO, this study adduces evidence that by undermining the social conditions of innovative enterprise the value extraction efforts of financial interests in the United States enabled an outsider, Roche, to gain access to valuable US-based knowledge flows that it would have otherwise been far more difficult to attain.

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the world pharma leader in term of total revenues (US$70 bn) including sales from consumer health, pharma and medical device division. As far as the pharma product sales are concerned Roche outperforms J&J given the pharma revenues generated in 2015 respectively US$38.8bn vs US$31.4bn.

Expansion of European pharma companies in the US market

The postwar era of growth in the pharmaceutical industry has been an important enabler of recovery among many European drug makers whose access to major markets in the world had been disrupted during the Second World War (Quirke 2004; Chandler 2005). Such growth was also major stimulant for innovation among the American drug makers who had accumulated considerable skills and capabilities in the development and manufacturing of medicinal products but had lost a major consumer: the governments of the Allied forces in World War II (Chandler 2005; Godley & Hughes 2014).

Newly introduced innovative therapies in the 1950s and 1960s, such as antihypertensive, antibiotics, anti-inflammatories, tranquilizers, and antidepressants would quickly face competition in the market since organizational capabilities to develop competitive products were steadily converging among both domestic and foreign drug makers that competed in the United States (Landau et. al. 1999). Competitors in the U.S. drug market responded differently to a gradual decline in the profitability of conventional therapies due to increasing market competition and cost of drug development in addition to declining macro conditions of the U.S. economy in the 1970s (Achilladelis 1999; Chandler 2005).

While some companies decided to diversify into unrelated industries such as food/nutrition, medical equipment, cosmetics, etc., some others decided to merge with the competitor of a similar size to boost their sales and marketing operations and strengthen their competitive position in their existing markets. Recognizing the potential of the fledging new field in molecular biology, some drug makers however made a strategic decision to steadily transition away from organic chemistry into biochemistry.

Such strategies devised and executed to challenge the uncertainties concerning the changes in the pharmaceutical market and drug development technology through engaging in collective and cumulative learning activities in the emerging fields of molecular biology and biochemistry in the 1970s through 1990s would ultimately have varying impacts on the economic performance of the drug makers. In the following section, the current innovative performance of the leading drug makers in Europe is systematically examined to assess the economic outcome of pursuing such an innovation strategy in recent decades.

As current and future sources of profit, the current state of the product portfolios and pipelines possessed by the leading drug makers in Europe are recognized as a proxy for measuring the outcome of their past innovation strategies. As the most innovative and profitable segment of the pharmaceutical product market, only the prescription drugs, for human health, are taken into account for the analysis in this study. In addition to their lower ranking in the product value chain, over-the-counter (OTC) medications were excluded from the portfolio and pipeline data, given that such products are reported as separate profit centers in company annual reports.

The product portfolio and pipeline data are mostly compiled from the Form 20-Fs filed by the subjects of this study. As foreign companies whose stocks are traded on the U.S. market, the companies are required by the SEC to submit Form 20-F in which extensive discussions of the state of product portfolios and pipelines are provided.

An extensive review of annual reports for 2015, the latest year for which the data were available at the time the analysis was conducted, revealed 159 pharmaceuticals from which the seven companies generated significant revenues, and 527 product candidates currently being tested for safety and efficacy through clinical trials for regulatory approval for marketing in the near future. For the implicit or inconsistent reporting of product candidates in preclinical stage, due to confidentiality reasons, early stage product candidates have been excluded from analysis.

The company annual reports often revealed very limited information on the origin of drugs analyzed in their product portfolios or pipelines. Country of origin and other basic information on the products examined have been mainly gathered from Springer's *AdisInsight*, a comprehensive database of drugs that are approved or being developed currently. Additionally, the publication for Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book) as well as the database for Acronyms & Abbreviations are comprehensive data sources made available by the Food and Drug Administration (FDA) that were accessed frequently during the data-gathering process.

The country of origin is determined by the location of an institution at which the key component in a product was discovered by an individual or team of scientists. Given that a significant portion of products were developed through external collaborations, or attained through acquisitions, the origin of a drug may or may not be the same company marketing the drug. The product launch date is the official marketing date of the drug granted by the FDA in the U.S. market. In the case that a drug was discovered through interinstitutional collaboration (i.e. company-company or university-company) the place of patent application were taken into consideration as the place of origin. In this case, the data for the applicant of the key patents were gathered from Google Patents website.

Additionally, various other resources such as medical journals, industry reports, biographies of inventors, and miscellaneous news and electronic contents have been examined during the data collection process, given that the current sponsor of a drug registered with the regulatory agency, the FDA, may not necessarily be the original source of discovery. Since the proprietorship of a key molecule in a prescription drug may have been transferred through various different mergers and acquisitions, a thorough investigation of various types of historical transactions was necessary to identify the origin of such drug.

The revenue figures included in the Table 1 reveal a diverse composition of concentration on pharmaceutical products among big pharma companies in Europe. Roche leads the competition among the other European companies in terms of total pharma revenues and net income. With a long history in high-volume product markets such as agriculture and industrial chemicals, Bayer's total revenues surpassed Roche's, whose core competencies have historically depended on the development of ethical drugs and specialty chemicals. Pharmaceutical revenues make up 78% of the company's total revenues while Bayer only generates 30% of revenues from pharmaceuticals.

Table 1: Pharmaceutical product revenues and % share in total revenues by the Top 7

Company (# of products analyzed)	***TOT. REV (€ bn) [b]***	***PHARM. REV. / TOT. REV. (%)***	***U.S. [N.A.] PHARM. [HC] REV / TOT.REV (%) [c]***	***REV. [159] / TOT. REV. (%)***	***NI / TOT. REV. (%)***	***R&D/NI***
Roche (23)	44,995	78	54	72	19	0.98
Novartis (20) *[a]*	44,437	62	34	49	36	0.50
GlaxoSmithKline (26)	32.775	60	34	45	15	2.37
AstraZeneca (30)	22,219	96	40	90	12	2.12
Bayer (15)	46,324	30	31	24	9	1.04
Merck KGaA (7)	12,844	54	39	38	9	1.53
Sanofi-Aventis (38)	34,542	73	49	59	12	1.19

Sources: Company SEC filings and annual reports

NOTES:

TOT REV: Total Revenues; PHARM. REV: Revenues from pharma products; U.S. [N.A.] PHARM. [HC] REV: United Staters [or North America] pharma [or healthcare] product revenues; REV. [159]: Revenues from 159 products identified for the study; NI: Net Income; R&D: Research and development.

[a] Novartis' above average net income performance in 2015 was a result of extraordinary increase in the pre-tax gains ($12.7 billion) from the net sales to third parties from discontinued operations including the sale of Animal Health ($4.6 billion) to Eli Lilly Company as well as the completion of series of asset swap transactions with GlaxoSmithKline (GSK) ($8.7 billion) including the sale of vaccine division in exchange for GSK's oncology drug portfolio and the creation of a joint venture over which over-the-counter drugs within the consumer healthcare division were transferred as part of the JV agreement. Net income/revenues ratio and R&D/net income for the previous year was 19.7% and 0.88 respectively.
[b] AstraZeneca revenues only include the sales of pharmaceutical products; Roche revenues include the sales of diagnostic which makes up 22% of total revenues; Novartis revenues include the revenues from Alcon (eye care) and Sandoz (generic/biosimilar) divisions which constitute 20% and 18% of total revenues respectively; Sanofi revenues include consumer health (10.1%), generic (3.5%) and vaccine (13.7%) revenues but excludes animal health; Merck revenues includes healthcare (54%), life science (26%) performance materials (20%); GlaxoSmithKline revenues vaccines (15%) and consumer health (25%); Bayer revenues include healthcare (49%); crop science (22%) and material science (26%). Excluding the consumer health revenues (20%), Bayer's pharmaceutical revenues made up only 30% of the group revenues.
[c] Bayer and Merck revenue figures are for the North America region. AstraZeneca, GSK, Sanofi and Bayer figures other healthcare products including consumer health products.
Also, any revenue figures published in foreign currencies are converted into Euros using the annual average of exchange rates in 2015 provided by companies in their annual reports. GSK figures in British pound, AstraZeneca and Novartis figures in USD, and Roche figures in Swiss franc were converted into Euros.

AstraZeneca appears to the only company whose focus is almost exclusively on the development of pharmaceutical products (96% of total revenues are generated from pharmaceutical products). Roche and Sanofi follow AstraZeneca with 78% and 73% concentration rate on pharma sales respectively. Despite pioneering in the field of ethical drugs in the late-19th and early-20th century, the two German companies, Bayer (30%) and Merck (54%), appear to be the least concentrated, or the most diversified, drug makers in the list.

The Table 1 also indicates higher net income ratios observed among the non-German companies that appears to be the consequence of larger concentration on higher value pharmaceutical products. Given the portion of pharma product revenues, the US market appears to be the major consumer of such premium products. Once again, Roche leads the European companies in taking advantage of highly profitable product markets in the US, with 54% of total pharma sales in the US in 2015. With nearly half of the revenues generated in the US, Sanofi-Aventis follows Roche in capturing value in the US pharma market.

Although the diversity attained by German companies seeks to maintain stability at the cost of lower operational profitability and slower economic growth, a strategy to focus heavily on pursuing pharmaceuticals, especially in the higher value segments, can pose a risk given that it would require a solid commitment to organizational learning and sustainable innovation practices to attain superior innovation competence and performance.

The 159 products identified for analysis constitute a significant portion of group (54%) and pharmaceutical market (65%) revenues and generated nearly €130 billion revenues globally for the top European companies in 2015. According to *EvaluatePharma* World Preview 2016, a popular periodical forecasting future economic trends in the global biopharmaceutical market published by Evaluate, a global healthcare market analytics firms based in London, the worldwide sales of prescription drugs in 2015 was nearly €700 billion in size and roughly 25% of that market consisted of prescriptions of orphans and generics. Such an estimate indicates that, through the marketing of those 159 products, anywhere from one-fourth to one-

fifth of the worldwide prescription market is being captured by the European companies identified in this study.

Placing the market share of the top seven drug markets in the global context illustrates the importance of sustaining innovative performance for global competitiveness in the biopharmaceutical industry. As an enabler of such performance attained today, one carefully needs to examine the sources of innovative capabilities in the past. The following analysis seeks to accomplish such goal. The following approach is an attempt to identify the sources of growth through tracing the path of learning back to its origin and by reverse engineering the process of innovation through which an innovative product is generated today.

Product portfolio and pipeline analysis

As discussed earlier, in the rise and decline of the European pharmaceutical industry in the first half of the 20th century, the expansion of the U.S. drug market aided the postwar recovery efforts of the European pharmaceutical companies. Since the U.S.-based research institutions were leading the global drug discovery efforts in the postwar period, major European drug makers were expanding their research operations in the major U.S. science and technology hubs such as New Jersey/New York corridor in the 1950s through 1970s and California since 1980s (Cohen 1986; Casper 2001; Quirke 2014).

In addition to completing the acquisition of pharmaceutical and biotechnology companies especially in the 1970s through 1990s, the top European companies were also active in pursuing drug research and commercialization deals to strengthen their share of the U.S. market. Such efforts are reflected in Figures 1a and 1b, illustrating the distribution of the total number of products and revenues generated by country of origin. Of the 159 products identified in the top seven European BP companies, 47% originated from the US (where the discovery of key drug component took place). Those products made up nearly half of the total product revenues in 2015. While the total number of products originating from Switzerland constituted only 11% of total products, revenues from such products made up 16% of total revenues. Such a ratio indicates that the products originating from Switzerland tend to be higher value-added therapies.

The pie charts in Figures 2a, 2b and 2c illustrate the breakdown of product revenues based on their origin in three distinct time periods based on the product launch dates. The time periods considered in this illustration reflect different drug discovery/development methods (i.e. random screening/synthetic chemicals; recombinant upgrades of existing products such as insulin/chemical or biologics; genomics and high throughput screening/advance biologics, etc.) that were employed by the BP companies at the time. This illustration compares the common discovery methods employed at the time of product launch. Such a distinction confirms that given that German and Swiss firms were highly competitive in organic chemistry Europe was the country of origin for chemistry-based products launched in the 1980s. But, in the era of biochemistry and molecular (1990s and 2000s), a new generation of biotechnology product emanated from the innovation networks in the US and UK.

While the drugs first launched in the 1980s were the byproducts of the organic chemistry era, the product launches in the 1990s included a new generation of recombinant therapies but they were often the re-engineered versions of molecules known to scientists at the time (and therefore were considered to be "low-hanging-fruit" such as human insulin, growth hormone, etc.) (Alafi 2013). More innovative and complex therapies such as monoclonal antibodies for oncological indications were mostly being introduced in the early decades the 21st century, particularly following the completion of early drafts of human genome mapping, made available by the Human Genome Project (Scannell et. al. 2012).

As indicated in Figure 2a, at least a half of the product revenues launched in the 1980s came from products of Swiss or German origin while the revenues from the U.S.-sourced drugs made up only a quarter of the total revenues from products launched in the 1980s. The ratio, of the revenues based on the sales of

products originating in the United States quickly jumped from 24% to 58% with the introduction of new generations of biochemical products in the 1990s. Within a decade, products originating in the United States began to make up a very significant portion of total pharmaceutical sales. A notable change is observed in the share of revenues from products originating in Switzerland and Germany, respectively, from 9% to 17% and 3% to 9% in the 1990s and 2000s.

As illustrated in Figures 3a and 3b, the products originating in the United States constitute 30% of the total products marketed by AstraZeneca while the same products contributed only 17% of total pharma product revenues. Products developed by Swedish Astra appear to be the major revenue generators for AstraZeneca, given that 17% of the products with Swedish origin make up 36% of total revenues. Products with U.K. origin are 40% of total products but only 23% of total revenues.

The other major U.K.-based pharma company, GlaxoSmithKline, shows even greater dependence on the sourcing of new products from the U.S.-based product development operation, as shown in Figures 4a and 4b. Half of the total products originating in the United States make up one-third of the revenues, while 38% of the products originating in the U.K. still make up 60% of total revenues. This result is due to the company's strong sales in established products such as therapies for respiratory conditions, epilepsy and infections obtained mostly through mergers and acquisitions in the U.K.

In the case of German companies, the graphical illustration of Bayer's product data, in Figures 5a and 5b, reveals some interesting results. The maker of the legacy over-the-counter pain killer, Aspirin, has been steadily increasing its presence in the prescription drug market. Such growth in market share appears to have been achieved through major acquisitions that the company has completed in the United States since the 1970s. Nearly 80% of products marketed in 2015 came from the company's U.S. acquisitions such as Miles Laboratories, Berlex (which came with the acquisition of Schering AG, another German company with a major presence in the United States under the name Berlex Laboratories) or technology collaborations with companies such as Regeneron, Onyx and Chiron. The products originating in the United States made up 91% of the company's prescription drug sales in 2015.

The data for German Merck, also known as Merck-Serono, also reveal an interesting case, with 14% of total products originating in Germany generating 6% of prescription drug revenues. As illustrated in Figures 6a and 6b, the acquisition of Swiss Serono, a leader in reproductive health field, appears to have boosted the product portfolio, with 43% of products, constituting 57% of product revenues, originating in Switzerland and the other 43% from the United States contributing 3% of total product sales. As a company with significant R&D operations in the United States, it is likely that some portion of that 43% product ratio was enabled by the R&D capabilities developed through the company's U.S. operations.

The graphics in Figures 7a and 7b illustrate the analysis of product data based on the country of origin. Sanofi-Aventis, the only French company included in the study, also appears to have boosted its product sales by acquiring one of the very few large dedicated U.S. biotechnology companies, Genzyme, in 2011. Of the total products in its portfolio, 39% originated in the United States, with a significant portion of those originating in the U.S. having been obtained through the Genzyme acquisition. The data also show that 26% of those products originating in Germany came through a series of mergers; first the merger of Hoechst AG with the French Rhône-Poulenc in 1999 to form Aventis and the merger of Aventis with Sanofi-Synthélabo in 2004. The products with German origin made up 42% of total pharmaceutical sales in 2015.

As discussed earlier in the historical background of the pharmaceutical industry in the postwar period, Swiss companies were the first explorers of the fledging biotechnology from the early years of enlightenment in molecular biology. Today, Novartis, formed in 1996 after the merger of Ciba-Geigy and Sandoz, is one the world's most successful biopharmaceutical companies in terms of financial and

innovative strength. Among all the other top pharma companies in Europe, Novartis has the largest number of products that originated in the company's R&D operations in Basel, Switzerland. As illustrated in Figure 8a and 8b, of the total products marketed, 65% originated in Switzerland, contributing 69% of the company's total pharmaceutical revenues in 2015.

The reason for such success could be the company's clever strategy to pursue close collaboration with the top scientific establishments in the United States through generous support provided by the Genomics Institute of the Novartis Research Foundation (GNF) since the late 1980s. A notable relation that GNF forged with The Scripps Research Institute (TSRI), one of the nation's leading biomedical research institutes at the time, was instrumental for facilitating interaction between academic and industrial scientists from the earlier years of the genomics revolution (Zeller 2004). Such learning efforts would later extend to pursuing partnerships with Chiron, the first company to clone molecules for the treatment of cancer and infectious diseases, in the 1990s before the company was acquired by Novartis in 2006.

Contrary to the product data on Novartis, 82% of Roche's products originated in the U.S. and contributed to 95% of the company's pharmaceutical revenues in 2015. As illustrated in Figures 9a and 9b, Roche's dependence on U.S.-based R&D operations should come as no surprise given that the survival of the company depended heavily on the expansion of the company's R&D operations in Nutley, NJ during the Second World War. Through the R&D operations at Nutley, Roche discovered and developed Valium, one of the very first blockbuster tranquilizers. Valium made Roche the largest pharmaceutical company in the world by the end of 1960s.

A significant portion of Roche's products are highly innovative new therapies co-developed through partnering in R&D with Genentech since 1979. A biotechnology icon of the 1980s, Genentech, arguably the world's first biotechnology company, is now a wholly-owned subsidiary of Hoffmann-La Roche. Roche became an important competitor in the biotechnology market through the company's close collaboration with Genentech in the past decades. Nevertheless, the company's interest in moving into biotechnology even predates the establishment of Genentech in 1976.

Roche has been making substantial R&D investments in basic and applied research in molecular biology since the establishment of the Roche Institute of Molecular Biology (RIMB) in 1967. Through this new addition to the company R&D powerhouse in Nutley, NJ, in which the company's legacy products such as vitamins, tranquilizers (namely Valium) were discovered, Roche would engage in extensive organizational learning in the fledging field of molecular biology. Such learning efforts at Roche depended on what Lazonick calls the social conditions of innovative enterprise, as examined extensively below.

An overview of the top European pharma pipelines indicates a similar performance that was observed in company-by-company analysis of the product portfolios. In terms of products nearing commercialization (products in phase III clinical trials or in the submission stage), the two Swiss companies show great strength in the development of late stage products. As illustrated in Figures 10c and 10d, nearly the half of late-stage product candidates belong to Roche and Novartis, so the two companies are likely to surpass the innovative performance of the other big pharma companies in Europe as far as new product launches are concerned in the near future.

After completing a busy acquisition season, the U.K.-based companies are populating their product pipeline with early stage candidates as illustrated in Figures 10a and 10b. Nearly the half of phase II candidates are pursued clinically by GlaxoSmithKline and AstraZeneca and a similar performance is observed among the phase I candidates, with nearly 41% coming of them being pursued by the two U.K. companies. However, Roche appears to dominate the competition among the seven European companies given that 34% of the phase I candidates pursued by the top seven are belong to Roche. The company

comes third after the after GlaxoSmithKline and AstraZeneca as Roche's phase II candidates constitute 17% of the entire phase II population identified for the seven European companies.

The study thus far has traced the products back to their origins and illustrated the importance of the U.S. not only as a major product market that has been the primary driver of profitable growth but also as the focal point for transforming organizational capabilities to remain adept in overcoming the hurdles of changing market and technology conditions. Innovating new therapies becomes more challenging as BP organizations' capabilities to capture and process knowledge are tested during the age of genomics due to oversupply of new information. Enabled by advancements in molecular genetics and computer science, the production of information can sometimes be greater than how much an innovative company can handle for timely processing and analyzing such information (Pollack 2010).

From the perspective of Chandler (2005), information overflow in the genomics age requires much greater economies of speed to keep up with such learning challenge. Only a small group of big pharma companies have been consistently investing in the building of new learning bases to make the radical move into the biotechnology market since the early years of the molecular biology revolution. And the top performers in the global drug market today are leading the race in biopharmaceutical innovation.

Earlier analysis of product portfolios and pipelines revealed that Swiss drug maker Roche appears to be leading the race. In the following section the study will examine the process by which Roche remarkably transformed organizational capabilities to transition into the biotechnology segment despite having no relevant skills and capabilities in biology to encourage and facilitate such transition. Through an extensive case analyses, the study will explain how and why Roche attained such a transformation to become a market leader in the biotechnology.

INNOVATIVE ENTERPRISE AND SUSTAINABLE GROWTH: A CASE ON ROCHE

This study utilizes the *historical-transformation methodology* as the basis for the case-based research approach on how Roche successfully managed to transform organizational capabilities to capture the new biotechnology market and achieve remarkable growth through such a transformation. As explained by Lazonick (2002), the utilization of such methodology is key to explaining why economic performance varies from firm to firm over time as those firms continue to operate within the same institutional environment and macroeconomic conditions and face similar technological and market challenges.

In the following section, this study addresses such questions in the context of the European biopharmaceutical industry through the case analysis of Hoffmann-La Roche, a Swiss pharmaceutical company whose innovative performance transcends today's industrial standards after surviving through multitudes of crises stemmed from issues or events concerning the economic, political, technological and market environment of the period. The historical-transformation of Roche is a remarkable illustration of why and how the social conditions come into play when the innovation process in a business enterprise faces challenges that stem from the changes in the market and technology.

By applying Lazonick's theory of innovative enterprise framework, the research will examine the impacts of financialization on organizational integration, strategic control and financial commitment, which constitute the basis for building and sustaining productive capabilities in innovative organizations. When considering these social conditions in the context of biotechnology, the US industry's prevailing business model appear to be counterproductive in delivering superior innovative productivity.

Analytical perspective

In this study, the financialization hypothesis will be applied in an attempt to explain the productivity challenge of the BP industry in the U.S. Similarly, Lazonick (2009) explains financialization as a transformation of business organizations from the *Old Economy Business Model* (OEBM) of the post-World War II decades to the *New Economy Business Model* (NEBM) that emerged with the rise of the information-and-communication technology industry in the U.S. during the 1980s and 1990s.

Lazonick (2014) argues that the transformation to NEBM was accompanied by the rise of maximizing shareholder value (MSV) ideology because of the reliance of ICT and biopharma firms on the speculative NASDAQ stock market to attract venture capital, which could exit through a quick IPO on NASDAQ, and high-tech labor, which could be induced to leave secure employment at Old Economy companies through stock options as a form of remuneration at the New Economy companies.

As a popular management concept that has become dominant in the United States since the 1980s, MSV considers the enhancement of shareholder value as the top management priority. But MSV is a theory of value extraction, not value creation, and hence such ideology is pursued at the expense of productive capabilities in the economy (Lazonick 2017). Lazonick (2009) reveals the contrasting characteristics of the old and new economy business models categorized in three generic activities in which businesses engage: *strategy* (concerning issues such as what goods or services to pursue and how to produce them), *finance* (how to finance production process); and *organization* (how to recruit and retain the right talent and integrate the talent pool to sustain the organizational value-creation efforts).

In a financialized business model, what Lazonick and O'Sullivan (2000) characterized as *downsize-and-distribute* is the prevailing resource-allocation regime that supports value extraction activities often pursued in the name of enhancing shareholder value and at the expense of productive capabilities within business organizations. An innovative enterprise on the other hand rather pursues a *retain-and-reinvest* resource-allocation regime that supports value-creation efforts within the organization and ultimately, if successful, may reward all parties who contributes to the process.

As a theoretical tool used in understanding the growth and performance of the firm, the *theory of innovative enterprise* (TIE) provides a relevant and rigorous account of how business organizations create value and improve their economic performance in real economy. Through TIE, Lazonick conceptualizes a theory for the firm that achieves growth through productive transformation and explains how an innovating firm obtains resources and transform them into revenue generating goods and services that are higher in quality and lower in cost. Unlike the neo-classical "optimizing" firm whose economic growth is constrained by the resources available to the firm, the "innovating" firm uses organizational learning to overcome the challenges that stem from constraints on resources for creating competitive advantage and a path to sustainable growth.

In order to capitalize on a market opportunity, or to explore and conceptualize new ones, an innovative entrepreneur or manager would need to engage in three fundamental activities: conceiving, designing and executing an innovative strategy and engaging in organizational learning to develop and utilize resources and to coordinate innovation efforts; [acquiring] finance to procure, develop or utilize resources and to sustain the innovation process until it delivers the intended outcome; and forming an organization where the process is embedded and facilitated. The process of productive transformation is important because it ultimately leads to innovation, which, in Lazonick's terms, is the generation of "higher quality products at lower costs than had previously been available".

In an innovative enterprise, Lazonick argues that *strategy*, *organization*, and *finance* have to be formulated and implemented carefully to confront the challenging characteristics of innovation, which is:

uncertain (no return is guaranteed when investing in the innovation process); *collective* (innovation cannot be done alone, but requires collective learning efforts among individuals with varying skill-sets); and *cumulative* (innovation takes time to accumulate the necessary skills and knowledge) (Lazonick, 2015).

The social and complex nature of the innovation process requires the conceptualization of a new theoretical framework that possesses the necessary capabilities to capture such complexity around tangible conceptus and measure the innovation performance based on the evidence manifested in socio-business indicators. As a response to this theoretical challenge, Lazonick offers three organizational concepts, known as *social condition of innovative enterprise* (SCIE) as a theoretical framework for the assessment of the economic performance of business organizations.

The three social conditions, *strategic control* (SC), *organizational integration* (OI) and *financial commitment* (FC) are instrumental to the systematic analysis of organizational performance. SCIE implies a set of relations that empower managers in the resource allocation decisions who are committed to the innovation process (SC); incentivizes people from different functions and capabilities to dedicate their skills and efforts in achieving strategic objectives (OI); and ensures that the necessary funding is committed to the innovation process until the intended financial returns are generated through sales of an innovative product (FI) (Lazonick 2015).

The adoption of a financialized business model would ultimately inhibit innovation, and thus the economic performance of an innovating enterprise and the entire productive economy. As *value-extracting* activities increase, the social conditions of innovative enterprise ultimately change to the extent that they no longer effectively support innovative strategies, organizational learning efforts, and sustained committed finance.

After adopting a financialized business model, *value-extraction* mechanisms, aided by MSV ideology, incentivize top management to pursue a *downsize-and-distribute* resources-allocation regime. This regime reconfigures resource allocation strategies to free cash-flow (in the name of capital efficiency) by "downsizing" (i.e. cutting costs, layoffs, outsourcing, liquidating assets, etc.) and the freed-capital can be "distributed" not only as dividends to shareholders but also as gains to *sharesellers* who time the buying and selling of shares by artificially boosting stock prices through stock repurchases.

Innovative enterprise in the age financialization: A case study on Swiss-based Roche Group

In 1893, with the financial support of his father who was a wealthy silk merchant, a young Swiss banker from Basel Fritz Hoffman La-Roche invested 200,000 francs in Bohny, Hollinger & Cie., a small chemical manufacturer in Basel, Switzerland (Roche). As an entrepreneur who envisioned a blooming future for the innovative marketing of branded pharmaceutical products, Hoffmann's disagreement over the management of this chemical factory ultimately led to the acquisition of the factory together with the company's Munich-native pharmacist Max Carl Traub to form Hoffmann, Traub & Co. in 1894. F. Hoffmann La-Roche and Co. was first incorporated after Hoffmann and Traub decided to part ways in 1896, shortly after establishing the company's first foreign subsidiary in Grenzach, Germany (Peyer 1996).

Although Fritz Hoffmann envisioned building an innovative enterprise, his journey to such a goal wasn't an easy one from the very early days of Roche. Despite introducing no successful product in the market yet, Fritz continued to established new subsidiaries and invested heavily in building a capable research facility to ensure developing high quality products. Since the new product launches were delayed as the investment in capital expenditure increased, the company faced bankruptcy only years after its incorporation (Roche).

Fritz managed to recapitalize the company with funds generated from family members and hired a talented young chemist, Dr. Emil Christopher Barell, and an apothecary, Carl F. Schaegers, who helped Fritz to develop and introduce a series of new products and Sirolin, a flavored cough syrup (Bürgi & Strasser 2009; Roche). The growth achieved through the successful launch and marketing of Sirolin urged Fritz to maintain his internationalization efforts in the early years of 1900s. By 1912, Roche managed to quickly establish its presence in many major markets, including the first sales office in New York in 1905 (Peyer 1996).

Despite introducing highly innovative new products such as a heart tonic (Diagalen) and a pain killer (Pantopon) in the market, the growth followed by the launch of those successful products was hampered by the onset of the Great War. Roche's products were boycotted both by French and Germany consumers, blacklisted for continuing to do business with the both enemy nations. Additionally, the company's access to the production facility in Grenzach, Germany, where the majority of production took place, was restricted. Additionally, Roche lost one of its most important markets, and some major assets along with it, during the Russian Revolution of 1917.

The toll of the Great War and the Russian Revolution was heavy and once again the company was facing the threat of bankruptcy in 1919 (Roche). In dire need of capital, Fritz Hoffmann decided to restructure the company to a limited partnership and accepted outside capital to form F. Hoffman La-Roche & Co. Ltd. Emil Barell and some other associates also invested in the new limited partnership, and with the financial backing of Basler Handelsbank that was headed by his brother-in-law Rudolf Albert Koechlin-Hoffmann, Fritz Hoffmann manage to recapitalized the company and overcame a insolvency issue in 1919 (Peyer 1996).

Maintaining the Roche vision and strategic control in the interwar era: F. Hoffmann La-Roche & Co. Ltd. under the control of Emil Christopher Barell the "innovator"

The challenges Fritz faced in the early years of his growing company took heavy tolls on his health and at the age of 52, Fritz Hoffmann passed away in 1920. Upon Fritz Hoffmann's death Dr. Barell was appointed as the new managing director of Roche. Upon acquiring the interest of Fritz Hoffmann and Adèle La Roche's younger son, Alfred Hoffmann La-Roche, in the company, Dr. Barell became a major shareholder and took over management. In addition to being a young bright chemist and innovator, Dr. Barell became one of the largest shareholders, after the Roche family, and the new leader of the organization an ailing company trying to recover from the calamities of the recently ended Great War (Roche). He was known to be a very tough manager who often applied harsh austerity measures to restructure the company for a path to healthy growth during the period following the war.

Despite the hefty restructuring measures imposed by Dr. Barell early in his tenure as the new managing director, the research division at Roche, under the leadership of Markus Guggenheim, managed to launch more innovative products in 1920s, most notably the company's first semi-synthetic product, Allonal, a sedative marketed as a sleep aid. In the meantime, Dr. Barell appointed Elmer Holmes Bobst, who was initially hired as a salesman at the New York office in 1911, to became the manager and treasurer of the Hofmann La-Roche Chemical Works by 1920. To capture a greater share of the fast growing U.S. drug market, Bobts restructured the small sales office in New York into an independent subsidiary before relocating the U.S. operations to its new home in Nutley, New Jersey in 1928. (Peyer 1996)

During the interwar years Dr. Barell was successful in recruiting highly talented scientists and chemists such as Tadeuszs Reichstein. Reichstein, a young scientist at the Swiss Federal Institute of Technology in Zurich accidentally synthesized vitamin C while trying to synthesize the aroma of coffee at his laboratory throughout the most part of the 1920s (Steffen 2012). Once he had successfully manage to synthetize a

form of Vitamin C in 1933, Reichstein began to search for the right industrial partner to adopt his revolutionary synthesizing technique for the mass production of Vitamin C (Steffen 2012).

In 1933, Roche and Reichstein joined forces to develop a new production process that allowed the company to scale up production without causing bacterial contamination in the production site (such methods are often referred to as the Reichstein process), a manufacturing issue not many other competitors seemed to have resolved at the time (Roche). Another chemist hired in 1936 from ETH in Zurich, Otto Isler, was assigned to find new synthetic pathways to vitamins eventually led the company to be the largest producers of vitamins in the market (Bürgi & Strasser 2009))

The economic success achieved by the introduction of the first synthetic chemicals, Allonal and vitamin C, urged management to intensify the research focus in developing new products through synthesizing new chemicals. Hence a shift in focus into synthetic chemistry resulted with the increase of investments in the company's in-house R&D capabilities. The company's employment of research personnel went from 26 researcher in 1924 to 75 in 1944 (Bürgi & Strasser 2009).

Challenges with maintaining organizational integrity during the Second World War

On the eve of the Second World War, Roche made radical changes in the ownership structure of the firm to ensure that the company's operations would be sustained in the case of complete Nazi occupation of continental Europe. While responsibilities pertaining to the operations of continental Europe were assigned to the interim wartime Swiss headquarters in Lausanne, the operations in the rest of the world, including the subsidiary in the United Kingdom, were assigned to a newly created twin company, SAPAC Inc., based in Uruguay. This twin structure provided insurance against the potential loss of proprietorship in the company, in the case of a potential Nazi sequester of the assets of Roche in Europe, SAPAC Inc. could still operate independently (Kurosawa 2015)

After the German invasion of France in 1940, Dr. Barell decided to move to Nutley, NJ, from where he continued to manage the Group until the end of the war. In following Dr. Barell's arrival in Nutley, Roche assisted the relocation of many European scientists, many of them Jewish, to the U.S. Nutley site, which housed many Roche scientists from Basel. After the arrival of the European scientists Nutley site became an the most important R&D function of the entire organization that sustained the company's research efforts throughout the war (Peyer 1996; Bürgi & Strasser 2009; Kurosawa 2015). In addition to generating two-thirds of Roche's overall profit, thanks to the growth of the U.S. market during the interwar period, the U.S. subsidiary, Roche-Nutley employed nearly the half of the Roche global workforce by 1945 (Peyer 1996; Kurosawa 2015).

Top management faced major difficulties in maintaining the integrity of the Group during the war. Despite the surging demand for drugs particularly vitamins, maintaining profitability, or even achieving economic growth, was hard to come by as access to the production sites in Nazi-occupied territories was highly restricted and the mobility to move goods and personnel across Europe was highly uncertain and costly. The subsidiaries within the Nazi-occupied territories attempted to declare independence from the Group. However, Dr. Waldemar Hellmich, the head of Roche Grenzach in Germany, managed the affairs with the leadership within the subsidiaries to maintain the ties with these subsidiaries intact (Roche; Peyer 1996).

As the most profitable unit within the Group, the management within the U.S. unit, under the leadership of Elmer Bobst, prepared for a spin-off but such attacks against organizational unity was repelled by the efforts of Alfred J. Fuchs, the director of finance (Peyer 1996). In 1944, Elmer Bobst retired from Roche-

Nutley as the nation's highest paid executive at the time and took charge of William Warner Company shortly after his departure from Roche-Nutley (Moritz 1973).

Although the reasons for the managerial revolt at Roche-Nutley have never been examined extensively, it shouldn't be difficult to identify the nature of disagreement between U.S. management with the global leadership from Bobst's publically expressed concerns over his pay and work conditions in his autobiography:

> *I was so regularly underpaid and overworked . . . that . . . when I reached a position where I could do something about decent working conditions and generous employee benefits in the pharmaceutical industry, I did. (Bobst 1973)*

Success in synthetic chemistry doesn't satisfy Roche's scientists: Post-war period marks an important turning point in Roche's near history

Roche's recovery efforts at the end of the Second World War were hastened with a new application found for vitamin B in the field of haircare in 1945. The new application in the haircare was launched through a new subsidiary, Pantene AG, which turned out to be one of the major entities in successfully completing the post-war recovery efforts. Dr. Barell's return to Basel in 1946 signaled the beginning of a normalization period and the company managed to develop innovative new therapies such as *Gantrisin*, a sulfa drug for the treatment of bacterial infections, and *Rimifon*, another antibiotic for the treatment of tuberculosis mainly developed by the scientist at the Nutley laboratories.

After the death of Dr. Barell in 1953, the company's finance director Dr. Albert Caflisch became the new leader of Roche. During his tenure Caflisch replaced the Barell-era autocratic management practices with a more liberal leadership vision that would align with the building of the more modern corporate structure he envisioned for Roche as the company continued to its internationalization efforts in highly competitive drug markets. Such practices entailed more functional and regional autonomy to empower local leadership to pursue a long-term growth vision driven by innovative practice.

Dr. Caflisch was also concerned about the highly decentralized and fragmented R&D operations concentrated in three major centers: Basel, Switzerland; Nutley, New Jersey USA; and Welwyn, UK. Established in 1956 as a small global research strategy group, comprised of eight members including the top research and operation leaders of the major R&D centers, Roche Research Management Group (RRMG) was responsible for coordinating the company's fragmented R&D operations which was a consequence of the company's deliberate strategy to safeguard the organization's Basel assets and operations against a potential occupation of Basel by the Axis Powers (Bürgi & Strasser 2009).

A discovery of Leo Sternbach, a Polish research chemist who was transferred from Europe at the onset of the Second World War, would mark another turning point in the history of Roche in 1960. Desperate for a big hit in the early-1950s, Roche management requested Dr. Sternbach to synthesize a similar compound to the popular anti-anxiety drug, Miltown, developed by Wallace Pharmaceuticals (Tone 2008). However, instead of pursuing such a "boring" task, Dr. Sternbach decided to return to his earlier work, without informing his superiors, on some compounds that he had studied back in his native Poland to discover some new dye applications, which ultimately led to the discovery of benzodiazepine, a compound with chemical properties that demonstrated sedative effects. (Maugh 2005).

Since the work was done in secrecy, Dr. Sternbach waited for a while to find the opportunity to share his discovery with Lowell Randal, the head of the pharmacology division at Roche-Nutley, for conducting the

initial experiments on animals, which ultimately led to the discovery of Librium. Years of intense work on the new chemical compound by the Sternbach and Lowell studies led to introduction of a new tranquilizer branded as Librium in 1960.

Shifting the focus of drug discovery from chemistry to biology: Factors requiring drug manufacturers to transform drug research and development in the 1960s and 1970s

Some important events were unfolding in the post-recession period of 1930s with the foundation of a soon to be rising field of molecular biology. With the enactment of the Ransdell Act, the former the Hygenic Laboratory, a public laboratory initially established for bacteria study in 1885, was reformed into National Institutes of Health to become an important supporter of medical research in the U.S.

In the same period various different philanthropic organizations turned their attention to medical research and provided major support, through the NIH or independently, for healthcare research efforts (Robinson 2001). Among various different philanthropies, the funding from the Rockefeller Foundation was especially notable for the support of the fundamental research in natural sciences, particularly in the molecular biology, that was critical for the birth and growth of this new field in 1930s and 1940s (Weaver 1961; Abir-Am 1982; Fredrickson 1991).

The surging demand for penicillin and vaccines in the Second World War stimulated the academic/industrial drug R&D efforts in the Allied nations, namely the United States and the United Kingdom, and the winners of the wartime penicillin challenge managed to scale up their R&D efforts in the years following the war (Bud 2005; Quinn 2013). Those who were excluded from the wartime penicillin programs had further advanced their knowledge-base in organic chemistry and built an extensive libraries of newly synthesized chemical compounds during the postwar era (Bürgi & Strasser 2009).

However, the screening of such libraries of compounds against a wide array of biological targets, along with conducting clinical tests for potency and toxicity in living organisms, was increasing the cost of drug discovery in the absence of a radically different approach to the conventional “random” or “ programmed” screening of newly synthetized compounds in the 1950s (Galambos & Sturchio 1998). In the absence of further substantiated insight into pathology and pharmacology, the conventional drug screening tools were becoming bottleneck for the discovery of innovative new therapies. Given the advancements achieved in biochemistry and biology in the first half the 20th century, biochemistry was about to challenge organic chemistry for its superiority in drug discovery and development (Galambos & Sturchio 1998).

A medical tragedy came to light in 1962 when thousands of babies born with defects in various European and Commonwealth nations was caused by a sleeping pill considered safe for pregnant women, Thalidomide, developed by German Chemie Grünenthal. In the wake of this tragedy, the U.S. government accepted a comprehensive drug safety measure through the enactment of the U.S. Kefauver Harris Amendment in 1962 (Temin 1980).

By amending the Food, Drug and Cosmetics Act of 1938, this policy shifted the burden of proof from the FDA to drug companies and required the drug companies to provide the necessary evidence for drugs to be safe and effective before they could be approved for marketing. The new regulatory pressure to produce evidence for safety and effectiveness of a new therapy intensified the pressure on drug manufacturers to question the sustainability of their existing innovation strategies and make the necessary investments in knowledge acquisition and capability improvement (Bürgi & Strasser 2009).

Preparing for post-Valium period: diversification on a grand scale!

A vast fortune of the 1960s and 1970s came from the success of introducing a series of psychoactive drugs, tranquilizers Librium, and the world's first billion-dollar medicine in 1960, and Valium, in 1963. Valium surpassed the success of Librium. By 1969 as it became one of the most popular psychotropic medications worldwide later known to be as "Mother's Little Helper" (Tone 2008).

Bürgi and Strasser (2009) observe that the difficulties with sustaining growth without exploring new approaches to drug discovery enabled by the advancements in the emerging new fields in biochemistry were pronounced more frequently in the reports submitted to RRMG throughout the 1960s. In these reports some leading scientists within the research centers, particularly in the US and UK research centers, urging top managers to consider making investments in basic research in biology.

Bürgi and Strasser (2009) extensively studied the changes Roche had adopted in 1960s as the pharmaceutical industry was about to enter one of the major turning points in its modern history based on an extensive library of communication materials recorded between the scientists, leaders of the research community and top management at Roche. Such communication materials analyzed by Bürgi and Strasser (2009) reveal how a group of scientists were concerned about the newly emerging technological and regulatory issues that would inevitably face the company in the very near future if the need for a radically different new approach to drug discovery were to be dismissed by the company.

Aside from biological screening of synthesized chemicals, Roche had accrued very limited skills in developing manufacturing processes through employing biological means and capabilities in drug discovery and development, facilitated by an extensive learning efforts in the emerging fields of biology such as biochemistry, immunology and enzymology (Bürgi & Strasser 2009).

In the reign of organic chemistry responsible for the innovation of the company's legacy products, the leadership for crafting research strategy was reluctant to engage the organization in new learning programs in the emerging fields of biology for the most part of the 1950s and 1960s. Such apathy in biological learning resulted in the company's withdrawal from emerging new markets. Given its limited knowledge in the field of biology, the Roche researchers were concerned with the risk associated with the fermentation process for producing biosynthetic antibiotics, and hence decided to opt out of e biological drug manufacturing, an emerging new market in which major competitors such as Merck and Pfizer were building capabilities at the time (Peyer 1996).

Similarly, the research team dismissed the idea of manufacturing vaccines and antivirals, given that they can't be manufactured synthetically. Therefore, instead of investing in organizational learning for vaccine development and manufacturing, a potentially faster route to developing effective treatments for viral diseases, the leadership decided to adhere to the organic chemistry approach for the development of chemotherapeutic compounds. Such efforts in the antiviral program ultimately failed to deliver the anticipated productivity and capture a significant share in the emerging antivirals market.

While the company's recent attempts in entering new markets failed miserably, a group of scientists from Welwyn offered a gloomy perspective on the prospect of business growth based on the chemistry-focused traditional drug discovery approach. In a series of reports submitted to RRMG in 1966 the scientists from Welwyn raised major concerns, echoing the growing sentiments among the scientists in the other research centers, with a growing managerial apathy in biological learning could have detrimental effects on the long-term growth of the company (Bürgi & Strasser 2009).

The Welwyn report stressed the fact that top management had to make major investments in basic biological research that would ultimately eliminate the need for increasing investments in the random

screening of a growing library of synthesized chemicals as such screening efforts were failing to deliver the anticipated productivity in drug discovery (Peyer 1996).

Growing disparity between the number of newly synthetized chemical compounds and viable drug candidates based on the screening of growing number of chemicals was the most urgent issue to address among the leading pharmaceutical companies in the US. RRMG began to recognize the consequences of such a failure to fully engage in basic research in the emerging fields of biology as the company's early antiviral research program, lasting for the most part of the 1950s and 1960s, could only deliver a single compound given the chemical approach employed in the program without giving the necessary attention to acquiring biological insight into disease pathology and clinical pharmacology

Until 1960, the company's innovative capabilities were vested in organic chemistry, and the research leadership wasn't eager to join the post-war antibiotics and vaccine rush, given the company's limited capabilities in developing and manufacturing drugs through biological means. The company's leading chemists such as Otto Isler, the man behind the discovery of new synthetic pathways for vitamins, argued that the company's current success had been solely achieved on the basis of its competitive strength in organic chemistry that could be further strengthened for future innovation (Bürgi & Strasser 2009). Isler also argued that biological research was merely based on theories or speculations so that the idea of pursuing fundamental biological research would not result in new drugs, given its impractical nature.

A slow start in engaging in fundamental biological research: Establishing biochemical virology section at Nutley

The members of RRMG begun to play an integral role in devising and overseeing innovation initiatives and organizational learning efforts in the ways in which new drug discovery, guided by the newly emerging knowledge in biochemistry, could be pursued at Roche. In following the company's transition in drug development, from chemical extraction compounds from natural substances to deriving organic compounds employing tools made available by organic chemistry during the interwar period, Roche became the world's largest drug producer in sales by 1967, given the enormous success that vitamins and sedatives brought. Such success resulted in a financial windfall and global recognition among the international science community. This financial and reputational capital could be deployed in supporting organizational learning efforts while attracting world-class scientists to join such learning by forging much closer relationships with the academic research centers.

Although getting top management to prioritize the investments in fundamental research in biology, and to commit resources to fund such a long-term learning strategy poised a great level of uncertainty, was a tall order, the efforts of those visionary scientists at Roche were aided with the rising popularity of a new administrative-science paradigm, long-term planning, in the field of corporate management. Encouraged by the strong financial conditions, and the motivation to maintain its market position, top management established an independent committee as part of the research operations at Nutley to devise and oversee "long-range planning" for the organization.

A Rapid Change in Direction: Building the army of molecular geneticists through the Roche Institute of Molecular Biology (RIMB)

In 1967, Roche established RIMB as an independent research body within the company solely for the purpose of engaging in deep learning in the field of molecular biology at the most fundamental level. Among many individuals, Sidney Udenfriend, first director of RIMB; Herberth Weissbach; John J. Burns, executive VC; and Alfred Pletscher, VP of R&D at Roche in Basel who worked together in the same at the NIH in the 1950s, were key to the establishment of this institute (Udenfriend 1995).

Under the leadership of the nation's highly respected scientists, the Institute gradually evolved to be nearly indistinguishable from an academic-equivalent, given that the learning environment aspired to excel according to academic norms (Pollack 1982). Fostering such an environment had helped Roche to recruit top scientist in their fields, especially during the period when federal support for biomedical research was in sharp decline. The Institute hosted a number of international symposia on various different topics in molecular biology which created an ideal environment for academic and industrial scientists to exchange ideas that would benefit Roche immensely in the years to come (Peyer 1996).

In fact, the topic for the second symposium in 1973 was the latest developments in recombinants genetics. The symposium was held in the same year that Stanley Cohen and Herbert Boyer had announced their success in cloning a gene through recombinant techniques. Four years later Boyer (along with Cohen) was presented with the Virginius D. Mattia Award during the RIMB Symposium in 1977 for their scientific achievements (Boyer 2001). The symposium was held around the same time that Dr. Philip Handler had announced Genentech's successful undertaking of cloning the first human growth hormone, Somatostatin. At this event, Boyer had the opportunity to discuss the progress achieved in cloning Somatostatin at Genentech and introduced the capabilities that this fledging new start-up possessed at the time to the scientists at RIMB (Boyer 2001).

Roche placed heavy emphasis on fostering such a learning effort through RIMB and continued allocating resources to keep this basic science program running while dismantling some other research programs and downsizing the Basel operations. The institute gradually grew in size from 70 scientists in 1967 to nearly 200 by 1975, and over 500 by 1987 (Bürgi & Strasser 2009; Weissbach 1987). Attracting high-quality postdoctoral research fellows was critical for staffing the institute with the right amount of high-quality biomedical scientists, who were still in short supply at that time, to pursue high-quality research.

As the only non-academic institute at the time operating as an affiliated research unit within an industrial organization, Roche took part in an international visa-program coordinated by the State Department for improving the mobility of academic researchers (Peyer 1996). RIMB developed a partnership with local universities to design a new Ph.D. program that would allow students to attend classes at the degree awarding institutions while pursuing their research at the labs within RIMB (Weissbach 1987). Although some basic research of a similar kind had already been established in the interwar years by DuPont, Merck & Co. and Squibb, the institute became one the largest organizations in research and training, particularly in the field of biomedical science, supported by the industry (Bürgi & Strasser 2009; Weissbach 1987).

Although management had no expectation for this basic research institute to produce results in the short-term, the scientists at RIMB managed to produce some important work that was successfully translated into commercial products. *Abu-screen* (a diagnostic tool for screening drugs of abuse) and *Roferon* (*interferon-alfa developed* through recombinant DNA) are among the most notable examples (Peyer 1996). However, the most important contribution of this institute was the building one of the most productive molecular genetics department at Roche, based on the people who were trained at the Institute.

The role that RIMB played within Roche was instrumental in the organizational learning efforts. Intellectual accomplishments within the institute were key to crafting the company's long-term growth strategies and steering into high-growth markets, based on the trajectories of the fledging molecular genetics field (Bürgi & Strasser 2009). Having the legacy of becoming one of the most innovative companies in the field of molecular genetics and possessing one of the most successful portfolios of recombinant products today can be credited to the research and training efforts of this institute.

As the visibility of the Institute grew, Roche was able to recruit some of the most prominent scientists such as Severo Ochoa de Albornoz, a Nobel laureate, who was the director of RIMB from 1974 to 1985, leading a large group of highly accomplished scientists (Peyer 1996). Sidney Petska was another important figure who was instrumental in the success of RIMB as a team of RIMB scientists under his leadership was one of the first groups in the US to isolate pure interferon.

For decades, RIMB would remain devoted to the Institute's original principles that the scientists at RIMB would be independent in the choosing of broad scientific questions, regardless of the timeframe involved, to pursue basic research as they would passionately do in an academic setting. It is the direct result of such devotion to scientific independence that constituted the most critical element of the Institute's successful recruitment performance. In his farewell letter to the Institute's director emeritus, Sidney Udenfriend illustrates the quality of talent RIMB housed at Nutley, NJ:

> *…RIMB's postdoctoral fellowship and graduate student programs are among its greatest successes. Close to 1,000 fellows and 40 graduate students will have passed through the institute during its lifetime. Of these, 20 are now chairmen of academic departments, 50 full professors, 60 associate professors, and many more assistant professors. One is a university vice president. About 25 are independent investigators or department heads in research institutes. About 35 serve in leadership roles in the pharmaceutical industry. Members of RIMB received many awards and honorary degrees.*
>
> *Most significantly, there were at one time (1986-1987) seven members of the National Academy of Sciences on the institute's staff, four (Herbert Weissbach, Ronald Kaback, Aaron Shatkin, and Alan Conney) elected solely for work carried out in Nutley. To keep this in perspective, RIMB's total staff of independent investigators averaged between 25 and 30. Of these, only 10 or so at any one time were full institute members (equivalent to full professor, the stage at which academy membership is generally awarded).* (Udenfriend 1995)

Notwithstanding the Institute's great service to the company as long as it lasted, the Institute's physical distance to the center of the molecular genetics network in California was becoming an important hurdle in attracting and retaining talent. In fact, the management at Roche was unable to find a suitable candidate to replace Herbert Weissbach, the Institute's last director whose retirement was fast approaching at the time (Udenfriend 1995). After the acquisition of Sytex in 1994, Roche decided to move the Institute to Palo Alto, where Sytex's US headquarters was located. Roche management was more confident that a more suitable candidate, especially in the field genomics, could be identified at the epicenter of ICT and genomics revolutions (Udenfriend 1995).

"Go West, Young Man": Roche joins the cloning rush on the west cost

Through a team of world class scientists at RIMB, Roche gradually embedded itself in the fledging network of molecular biologists and geneticists (Peyer 1996). Through this network, Roche had been monitoring the latest developments in gene cloning technology that was pursued by Stanley Cohen of Stanford and Herbert Boyer of the University of California San Francisco in 1973. Despite the promise of those scientific accomplishments, which would potentially disrupt the ways in which the discovery of drugs could be pursued, the majority of big pharma establishments, especially given the riches of penicillin and antibiotic era, overlooked such advancements in molecular biology.

The wider reluctance to explore the commercial viability of such a technology had some basis to it, however. Various regulatory issues revolved around the emerging new technology, given that public fear was raised over risks associated with the science of manipulating living cells on a molecular level. Some medical scientists urged the NIH to put together a guideline for geneticists to adhere to during the

experiments. Such concerns were echoed in different communities around the world, and the governments of few nations took the measure to an extreme by extremely restricting such work or discouraging the work from being performed.

As Switzerland was one of those nations that adopted strict guidelines for conducting experiments using recombinant DNA technology, Roche management decided to establish RIMB within the U.S. headquarters at Nutley, New Jersey. Under the leadership of Dr. Sindey Petska, a research group at RIMB joined the race to isolate pure interferon (alpha), one of the members of a protein group that was considered to be the silver bullet for the treatment of cancer at the time (Peyer 1996). Genentech, Cetus (later Chiron) and Biogen (in collaboration with Schering-Plough) were all working on the same protein, which would lead to the discovery of other members of the interferon family (beta and gamma) (Vettel 2013). During such innovation efforts, another Roche research team based in Basel discovered a new method of identifying different types of interferons. They presented significant applications in the field of diagnostic and opened a new growth path for Roche to pursue.

Roche, Cetus and Polymerase Chain Reaction (PCR)

Roche had been active in the diagnostics field since the 1960s but not in the capacity to lead the market. Such opportunities emerged in 1989 after the decision to collaborate with Cetus in development of the PCR method. The PCR method was considered to be revolutionary and was declared by *Science Magazine* as the most important discovery of 1989, given that such a method was outperforming the efficiency and accuracy of other diagnostic tools at the time. The diagnostic application of this method was powerful. A complex virus such as AIDS could only be detected through conventional blood tests months after the first infection. However with the use of the PCR method, the same virus could now be detected almost instantaneously (Peyer 1996).

Roche's acquisition of the PCR technology wouldn't have been possible if the management at Cetus had recognized its value and pursued such technology as a viable business opportunity (Rabinow 1996; Glaser 2006; Fore, Wiechers & Cook-Deegan 2006; Cohen 2009; Alafi 2013). Given the financialized business model adopted by Cetus had failed to develop the necessary productive resources (managerial, monetary or human capital) to deploy for the commercialization of the PCR technology. The impact of financialization on the innovation of the PCR method at Cetus that would lead to the acquisition of this technology by Roche is examined briefly.

The birth of Cetus, a venture-backed biotechnology company initially formed in 1971 and incorporated in 1973, was testament to a new technology-driven industry in which technology and finance were converging once again in the same fashion that was experienced throughout the evolution of ICT in Silicon Valley. Although Cetus was considered to be the first biotechnology company ever to be established in 1971, it did not become a truly biotech company until after Genentech emerged to develop recombinant therapies.

Moshe Alafi, lead investor and chairman, former academic and physician, Ronald E. Cape and Peter Farley, along with world-renown Nobel laureate in physics, Donald Glaser, co-founded Cetus with the initial purpose of providing commercial services for the fast screening of microorganisms using a device invented by Glaser to identify new antimicrobials. As a first-in-kind entrepreneurial initiative, Cetus managed to attract some major scientific figures as consultants such as two Nobel laureates Joshua Lederberg (for the discovery of bacterial conjugation) and Stanley Cohen (for the co-discovery of genetic engineering); the two influential figures at Mexico-based Syntex Laboratories Carl Djerassi and Alejandro Zaffaroni whose

successful collaboration on the synthesis of first oral contraceptive was key to the company's rapid growth in the 1950s and 1960 (Alafi 2013; Glaser 2006).

Despite possessing an all-star scientific advisory committee, a pool of scientific talent, and an astounding level of capital, secured through an all-time record initial public offering (IPO) for nearly US$120 million in 1981, Cetus suffered from lack of strategic vision, from very early on, for transforming technology and markets to pursue sustainable growth. The absence of such strategic vision constrained the organizational learning that ultimately resulted in the loss of other productive resources.

Various insider testaments reveal that Cetus was presented with various different opportunities to pioneer the development of novel biological therapeutics by employing the newly emerging techniques in the genetic engineering field. Despite recruiting Stanley Cohen, co-inventor of the recombinant DNA technique, as the top consultant, Cape and Farley, the top executives who were in charge of the organization's daily operations, were still insisting on pursuing a business line in providing commercial services to top pharmaceutical companies using Glaser's screening technology.

Despite all the efforts to attract a big pharma contract, Schering-Plough was the only drug company that decided to explore what Cetus and Glaser's new technology had to offer. Through this collaboration, Cetus agreed to assist Schering-Plough in the efforts to improve the production efficiency of Gentamycin, a powerful antibiotic used as a drug of last resort at hospitals in the most complicated cases of infections.

At the time, Bob Swanson was a member of board at Cetus, as a junior partner representing Kleiner & Perkins, and developed an interest in the recombinant technology presented by Cohen in various different occasions. Swanson approached Cape and Farley and asked them to hire him to pursue this new technology more extensively within Cetus. Not only was his request declined by Cape and Farley, Swanson was also let go by Kleiner and Perkins because, reportedly, the duo did not want a third partner. According to Vettel (2006) this was the second time Cetus declined a proposal to pursue recombinant DNA for pursuing Glaser's screening machine as Roche had approached the company to pursue this technology jointly a year before (pg. 212).

Unable to convince Cetus and parting ways with his former partners, Swanson decided to approach Herbert Boyer, the other inventor of recombinant DNA technique at the University of California San Francisco. Swanson pursued Boyer to explore the commercial applications of his disruptive technology through a new start-up with the prospect of securing a financial backing from Kleiner & Perkins. Not only did Cetus lose a talented technologist highly motivated to pursue the recombinant DNA engineering technology internally, they also created a fierce competitor that would later beat Cetus, and its successor Chiron, in the race to clone the top items on any biotechnology start-ups' to-do list in the late-1970s: first human growth hormone (*somatostatin* – a relatively small molecule in size) to be produced in bacterium in 1977, insulin in 1978, and growth hormone in 1979.

Cetus eventually decided to move into the cloning business when Genentech (1976), Biogen (1978) and Amgen (1980) all joined the race to pick the ripe fruits that were hanging low: human insulin, human growth hormone (HGH), interferon (alfa, beta, and gamma), etc. In response to the growing pressure from shareholders, the board decided to make some radical changes in the business model. Such a decision came with a shake-up of top management after completing the largest IPO ever recorded to date in 1981, when hiring the former president of Biogen, who would later replace Cape as the new CEO, upon the resignation of Farley in 1982 (Vettel 2006).

Cetus attempted to make the strategic leap into developing new therapeutics through forging strategic partnerships with other biotechnology start-ups. Through a R&D collaboration with a subsidiary of Royal Dutch Shell, Triton Biosciences, Cetus begun to pursue its first major therapeutic candidate, beta-

interferon b1 (Betaseron) in 1985 (Kinch 2016). However, after failing to show effectiveness for the treatment of the cancer agent, it would take years to discover that Beteseron could be an effective therapy for Multiple Sclerosis

Prior to the partnership on Betaseron, Cetus was already pursuing another anti-cancer agent, interleukin-2 (IL-2), in the early 1980s. During a fierce competition against Immunex, Genentech and a Japanese researcher, Tadatsugu Taniguchi, Cetus aggressively pursued the development of IL-2, and, in collaboration with the nation's leading IL-2 expert, Dr. Steven Rosenberg at the National Cancer Institute, pushed the new therapy through clinical trials (Lax 1985). In addition to boosting investment in R&D, Cetus was heavily investing in the expansion of manufacturing and sales & marketing operations to prepare the organization for the launch of this experimental new therapy that was still in the clinical phase (Lehrman 1992).

The cost of such an ambitious innovation strategy mounted fast as the clinical progress on interferon project was delayed. Fildes begun to sell the company's major assets in non-drug business lines such as a soon to be a major revenue generating technology, *polymerase chain reaction* (PCR), a technique for amplifying the production copies of DNA on a large scale that was discovered and developed by Kary Banks Mullis during his tenure at Cetus in the early 1980s that would win him the Nobel Prize in chemistry (along with Michael Smith) in 1993 (Cohen 2009; Alafi 2013; Glaser 2006).

From early on, Fildes was unable to recognize the importance of such a powerful tool with important diagnostics and research implications and decided to pursue the further development of this technology through partnerships as the popularity of such technology grew among the scientific community (Cohen 2009; Alafi 2013; Glaser 2006)). Cetus first formed a partnership with Kodak in 1986 for the development of an *in-vitro* diagnostic tool powered by the PCR technique, and formed a joint venture with Perkin-Elmer in 1987 to develop and manufacture the diagnostics instrument GeneAmp PCR Kit for biomedical research. (Fore, Wiechers & Cook-Deegan 2006)

As the expiration of the partnership with Kodak was approaching, Cetus was looking for new partner for the commercialization of PCR kits. Roche, a serious competitor in the IL-2 market that was getting ready for a legal battle in Europe as soon as *Proleukin* was launched in this market, showed significant interest in the PCR technology and agreed to discuss terms with Cetus for this technology. Given how much Cetus had invested in *Proleukin*, Fildes was willing to give up on PCR given that Roche had already acquired the marketing rights for IL-2 both from Immunex, a Seattle-based biotechnology start-up founded in 1981, and Ajinomoto, a Japanese company that held the IP rights for Taniguchi's recombinant IL-2 (Rabinow 1996).

Fildes was interested in avoiding any potential IP dispute against Roche as the company was getting ready to launch *Proleukin* (IL-2) in the Europe market for the treatment of kidney cancer. In 1989, Cetus agreed to license its PCR technology to Roche in exchange for marketing *Proleukin* in Europe without facing any legal action from Roche. Based on this agreement Roche would supply US$30 million cash to fund the PCR-based diagnostics research during the following five-year period in addition to purchasing one million shares of Cetus (Fore, Wiechers & Cook-Deegan 2006).

With the FDA's decision to disapprove interleukin 2 (IL-2) in 1990, an experimental cancer drug was considered to be the miraculous cure for Cetus' ailing financial health, the company was forced to proceed onto a new path as it faced a nearly $120 million loss mostly stemming from the risky bet on IL-2. In 1991, Chiron showed interest in the acquisition of Cetus for US$660 million worth stock-based transaction. However, the transaction depended on clarifying the legal dispute brought by DuPont concerning the validity of the PCR patents so the sale of the PCR business to Roche could be completed based on a deal

worth US$300 million cash in addition to subsequent royalties stemming from this technology (Rabinow 1996). Acquisition of such a powerful diagnostics tool would make Roche an important competitor not only in the diagnostics market but also in biopharmaceuticals, given its functionality in drug research, through which Roche would create an economic value measured in US$-billions in the years to follow.

Roche, Genentech and the First Generation of Recombinants Therapies

As Roche was pursuing the PCR technology to strengthen its position in the diagnostics market, the company was already pursuing different research partnerships on recombinant therapies with the other biotechnology start-ups in the region. At the time, recombinant *interferons* were considered as the silver bullets to fight cancer that could potentially become blockbusters quickly.

Although Genentech had the technology to clone such a protein, the company needed to acquire a protein source to initiate the cloning process. It turns out that Sidney Pestka at Roche had a cell line to source the protein since he and his team had been working on cloning such protein at RIMB. Given that Boyer had constructive talks with the management at RIMB a year before, at the time he was presented with the V. D. Mattia Award in 1977, Genentech decided to approach Roche to form a research collaboration with the research team at RIMB. Although this initial research collaboration was not productive, one positive outcome was that the management at Roche had begun to recognize the technological capabilities Genentech possessed while Genentech had discovered one of the best research partners to collaborate without the fear of losing the technology (Perkins 2002; Goeddel 2003; Raab 2003).

[Gen]etic [En]gineering [Tech]nology (Genentech), Incorporated

As young venture capital investment enthusiast who was trained in chemistry and management at MIT in the late 1960s, Robert (Bob) Arthur Swanson, first arrived in San Francisco to open Citibank's first west coast office for the recently established venture capital arm, Citicorp Venture Capital (CVC), in 1970. In the following years Swanson met with Eugene Kleiner, co-founder of the valley's legacy venture capital company Kleiner & Perkins, while serving as a board member in a nearly failed venture in which Kleiner & Perkins had an equity interest.

Impressed with his passion and abilities, Kleiner asked Swanson, who was only 27 years old at the time, to join Kleiner & Perkins as a junior partner in 1974. One of Swanson's first major assignment was to evaluate an investment opportunity at Cetus Corporation, the nation's first biotechnology start-up established a few years back. During Kleiner & Perkins' involvement with Cetus, Swanson had the opportunity to get to know more about genetic engineering and cloning from the company's world-renown scientific advisors. Although Swanson, and some other top science advisors and investors, were highly captivated by the commercial potential of this emerging technology, there was no imminent impetus to pursue such technology being acknowledged by management (Alafi 2013; Hughes 2011).

At the time Kleiner and Perkins were getting ready to let Swanson go (Perking 2002; Alafi 2013). Swanson asked Perkins to connect him with the top management at Cetus so he could explore a potential employment opportunity at Cetus (Perkins 2002). After his proposal to commercially pursue rDNA technology for Cetus got turned down by the company, he decided to pursue it independently, with a partner with the right scientific credentials and the seed capital promised by his former boss, Tom Perkins.

While surviving on unemployment benefits and still searching for a new job to sustain a decent living, Swanson was also assessing the commercial viability of the emerging rDNA technology and searching for a potential science-partner in the early months 1976 (Swanson 2001). After hitting it off quickly with Herbert Boyer and convincing him to partner in a venture to explore commercial opportunities using his

technology Swanson began his searches for identifying a potential product candidate and the two agreed to pursue the idea of developing human insulin and devising a plan to produce it.

The two decided to target the insulin, a molecule small enough to synthesize chemically, to mass manufacture using bacteria. The basic idea behind their value proposition mentioned in the first business plan was that such production of human insulin using rDNA technology would be a much more cost-effective way of producing insulin derived from animals (Swanson 2001; Hughes 2011). Given that the new venture was on a very limited budget and wouldn't be able to afford to build an ideal infrastructure to conduct experiments for proof-of-concept, Swanson decided to form Genentech as a virtual company, contracting with university scientists and facilities.

Boyer suggested collaborating with Arthur Riggs from and Keiichi Itakura, the two City of Hope scientists whose grant proposal for producing somatostatin, a growth hormone embodying a very simple amino acid structure, which was turned down by NIH, to make the human insulin. Riggs and Itakura were willing to make the human insulin but argued that it would make more sense to deal with a smaller molecule to test the idea. Although he wasn't very thrilled with the idea of following a small detour in the path to making insulin, Boyer and Riggs convinced Swanson to pursue engineering somatostatin as a proof of concept to demonstrate the world that rDNA was a commercial viability technology.

Swanson and Boyer each contributed US$500 to incorporate Genentech on April 7, 1976 (Swanson 2001). As the CEO, Swanson's first order of business was getting some funding to set up the contracts with the University of California, the City of Hope and Caltech for Riggs and Itakura to initiate the research. Kleiner & Perkins would initially invest $100,000, as agreed, for the completion of the legal work with the universities. With the infusion of additional capital from Kleiner & Perkins and other private equity/institutional investors, the total outside capital committed was around $1 million by the time the somatostatin experiment was initiated in February 1977 (Hughes 2011). By August, 1977 the first human growth hormone, *Somatostatin*, was successfully cloned.

At the time, the success in cloning Somatostatin was certainly considered as a major scientific achievement. However, there was even a more important implication of such achievement which was the visibility that such an event had brought upon Genentech and biotechnology in the late 1970s was invaluable. Before the study results were shared with the scientific community through an article pending for publication in *Science*, the president of the National Academy of Sciences, Dr. Philip Handler, had announced the results during his testimony before a Senate subcommittee studying gene research in November, 1977 (Schmeck 1984). Some additional endorsements from prominent figures in the scientific community followed Dr. Handler to praise the accomplishment and such high-level endorsements would uplift the public image of the genetic engineering that was unknown to most.

In the years following the *Somatostatin* success, Swanson was busy raising more money to hire new technical staff and start bringing some revenues from licensing and royalties. To clone the first human insulin was the top item in the agenda. A third round of fundraising was completed, new contracts were prepared and a team was assembled to start cloning human insulin. After its completion in August 1978, Swanson signed a licensing agreement with Eli Lilly for the commercialization of recombinant insulin. Genentech had followed a similar model for funding R&D and operations, and a revenue model for the commercialization of the next two products that the company worked on in 1978 and 1979: human growth hormone (HGH) for Swedish Kabi and *interferon-alfa* for Roche. Only A few years after its incorporation, Genentech managed to develop multiple products with which a modest revenue stream was established. Although there was no shareholder pressure to achieve operational profitability in the early years of its existence, top management insisted that the company's income statement should produce results around the break-even point, if not a very small amount of profit (Swanson 2001). Given

the heavy emphasis placed on gradually improving corporate financial strength starting from the break-even point, Genentech was developing engineering skills both in corporate finance and molecular genetics so that the company's R&D operations would be adequately funded without risking the integrity of shareholder equity and organizational productivity.

Swanson had hired his college roommate, Fred Middleton, as the company's first Chief Financial Officer. Middleton and Swanson had both attended classes in chemistry before pursuing a graduate education in business at MIT's Sloan School of Management, although Middleton had gone on to complete his graduate education at Harvard Business School. They both had spent some time in the consulting field before switching to finance.

The infusion of education both in engineering and finance at Sloan must have been the source of inspiration for engineering tools to address the corporate finance needs. Since the day it was incorporated, Genentech was envisioned to become a Fully Integrated Pharmaceutical Company (FIPCO) at some point in the near future. Such a vision and plans were explicitly spelled out in the company's early business plans first drafted by Middleton in 1979 (Middleton 2002; Swanson 2001). Fiscal responsibility was at the core of the financial operation to achieve steady growth. Any generated income was plowed back into funding the operations in product innovation.

The first genes that Genentech had cloned were relatively easy targets to achieve. The first major product, human insulin, was chosen deliberately because the molecular structure of insulin was already known to scientists and a major market was already established for such a product -- given that insulin was a recurring treatment of diabetes there existed a major revenue stream for Genentech (Swanson 2001). Since the safety and efficacy of conventional insulin had already been established, getting the FDA approval for the recombinant version couldn't be too difficult; at least that was what Boyer and Swanson had originally anticipated. By contracting out the work to be completed externally, Genentech could pursue product innovation without a major upfront investment in capital expenditures and full-time staff.

The lean operation model wouldn't had been sufficient for a company that aspired to become a FIPCO. After the insulin and growth hormone project, the company had to hire some full-time scientists to complete certain tasks in-house. Such tasks gradually became the company's core competence in winning contracts with big pharma and spinning out projects to form joint ventures. After the insulin project was completed in 1978, management decided to pursue multiple products simultaneous, which ultimately required increases in the size of the workforce. As the organization grew exponentially in the first years of its operations, the demand for new sources of finance increased significantly (Middleton 2002).

One way of generating new revenues would be through signing new contracts to out-license products. In return, the company could receive some upfront payments that would be followed by additional milestone-based payments plus some royalties down the line. Additionally, what Swanson and Middleton coined as *Pay-As-You-Go* (PAYG) is a product development partnership plan devised to appeal to the leadership at big pharma companies, given that such model would require a reasonable up-front payment and the rest of the payment would only be required if pre-defined milestones were to be achieved (Middleton 2002).

There were couple of important issues about the model. First, Genentech would still need to find new sources of funding to attain some working capital to maintain operations in between milestone payments. Second, meeting such milestones could create pressures on the workforce as well as the management given that making the payroll payments would depend on the receivables based on the upcoming milestone payments. And finally, as far as the products being cutting-edge, Genentech's had to rely on marketing partners in the successful translation of innovation into economic growth. After all, the size of

future royalty-based revenue streams would depend on the sales performance of the marketing partner. Additionally, such relations could be ill-pursued by the other party, which had occurred during a partnership deal with French Merieux in which the development process for hepatitis vaccine was deliberately slowed so that their colleagues at Pasteur Institute could launch their version and license it to Merieux (Swanson 2001; Kiley 2002).

Swanson was aware of the fact that PAYG wasn't the right path for Genentech to become a FIPCO, given that the products considered for out-licensing were major market products. If commercialized and marketed by the company than those products could have placed Genentech quickly on the path to become a FIPCO. However, Genentech neither had the resources to afford the costly clinical trials nor the sales and marketing workforce to launch any major product effectively. Therefore, PAYG was the way to go for a while as new product opportunities in rare diseases were being pursued for the purpose of forward-vertical integration and developing capabilities in product commercialization.

Given how little value was captured from the insulin deal that had granted an exclusive license to Eli Lilly for the production and marketing of insulin, management decided to pursue the idea of breaking up the market to negotiate separate licensing deals with multiple partners. Because the demand on recombinant products increased significantly after successfully cloning human insulin, management decided to negotiate multiple R&D contracts for the same product so that the product license for each major markets such as North America, Europe and Japan could be sold separately.

Pursuing such strategy to sell a product "three times" allowed Genentech to capture greater value from its innovative new therapies since negotiating separate deals entailed no cost increases. (Middleton 2002; Swanson 2001). If Genentech could only manage to finance the costly clinical trials, then the company would have the upper hand to negotiate better licensing deals, and better yet, market its own products in North America by building its own sales and marketing workforce (Middleton 2002).

In the meantime, Tom Perkins and some other shareholders had been seeking ways to liquidate their equity in Genentech. Given the success with insulin some shareholders approached Eli Lilly first and Johnson & Johnson next. Both companies declined the offer to pay around US$80 million to acquire Genentech (Perkins 2002). Unable to attract buyers to sell Genentech, its shareholder decided an IPO to be the best route for an exit event. Perkins had to pressure Swanson for some time to look into the option of doing an IPO soon (Perkins 2002).

Although skeptical at first, Swanson gave the green light for the investment banker to file the necessary paperwork with the SEC. Swanson (1997) argued that the reason he changed his mind was to beat Cetus in the race to become the first biotech company to go public. The Supreme Court had decided on the case for whether to patenting of genetically modified organisms, *Diamond v. Chakrabarty*, a few months before Genentech offered its stock on the New York Stock Exchange (NYSE) as the first biotech company to be traded in a major market.

Genentech's IPO on October 14, 1980, stirred a great market frenzy among investors, and Genentech's stock price rose to $88 from the opening price of $35 within moments after the stock began to be traded. Aspired to become a FIPCO in the near future Genentech had become the first PLIPO in 1980. The irony on such positive market reaction to a product-less biotech IPO can be captured in the following statement of the company's first CFO, Fed Middleton, explaining, in a way, the role of speculative markets in creating substantial financial returns for those who had made a leap of faith to work for a highly risky business venture:

> *I looked at all this [replacement of preferred stocks with common stocks] and tried to figure out a way of creating this incentive [a big bump-up on the value of Genentech stocks at the time of IPO]*

for new employees and management in a company that is already public. Companies continue to be risky. They only difference at Genentech was that we used to be a private company without products and now we're a public company without products. [laughter] Is the risk really that much less to an employee coming in? (Middleton 2002, pg. 59)

However, because such a high demand on stocks weren't anticipated by them, Swanson and Middleton had decided to sell only one million shares (up-o one percent oversubscription) to generate US$38 million. Money raised through the recent IPO would be used for building a production facility for growth hormone and *tissue plasminogen activator -tPA- (Activase),* a recombinant protein used for dissolving blood clots (Middleton 2002).

The financing plans for pre-clinical research and a production site were in effect. However the company was still in need of devising a financing plan for sponsoring the clinical trial for those products. Going after those two goals, targeting an orphan indication for the fast launch of products in small markets and being able finance the clinical trials to launch its own product, Middleton devised a new method called R&D partnership financing (RDPF) program. This was a highly complex financing method that was previously used among high-technology companies in the semiconductor industry (Middleton 2000). RDPF involved establishing R&D investment funds to function similarly to venture capital funds, as described in the following: Genentech establishes a new subsidiary as fund manager and starts raising capital for the new fund to finance the clinical trials for product candidate X. Middleton then goes out to raise funds as typical venture capitalists do.

Tax payers in high income tax brackets were usually attracted to such funds as tax shelters. Some of Genentech shareholders such as Perkins had invested in the funds at some point (Middleton 2002). An RDPF fund typically offered a royalty payment anywhere from five to seven percent over the period 12 to 15 years in addition to the R&D tax benefit based on the initial amount invested (Middleton 2002). For the riskier clinical programs a fund would offer the option of receiving 1,500 shares for the investment instead of a royalty payment option. In certain instances, the stock prices went up anywhere from 4 to 5 times and the investors decided to exercise their options (Middleton 2002).

The cost of clinical trials for the new generation Genentech products such as tPA, a new version of growth hormone and *interferon-gamma were* all covered by the funds generated through RDPF until 1986 (Middleton 2002). What made RDPF appealing to fund investors was the incentive that was available in the tax law. Such tax law in early 1980s allowed the companies' to pass along the tax benefit to their investors. Depending on the income tax bracket of investors, a portion of R&D expense accrued could be claimed as a dollar-for-dollar deduction against the profit generated.

Such an investment tool had been popular among high-income investors seeking tax shelters until the removal of such incentives with the enactment of the Tax Reform Act of 1986. Funding R&D through such funds appealed to Genentech shareholders because costly clinical trials had been finance without diluting shareholder equity and diminishing value. In fact, shareholder equity grew along with the economic value of intangible assets as the products progressed through clinical phases.

Management had been considering ways to start building sales and market capabilities by amending the R&D partnership on HGH with Kabi to launch this product in the US market. A new opportunity emerged as the company discovered a new therapeutic applications that had shown greater commercial prospect that the treatment of a pituitary dwarf (Swanson 2001; Middleton 2002). Given the initial market projections, HGH (Protropin), could be used in the treatment of a condition called *constitutionally delayed short stature –CDSS-* (a temporary delay in skeletal growth) and such marketing campaign in the US market appeared doable simply because there were around 500 pediatric endocrinologists who treat CDC

occurring among young children. Given that such specialists were spatially concentrated in certain medical centers, the product could be marketed by a small team of marketing staff (Swanson 2001; Middleton 2002).

The company considered a similar marketing strategy for the marketing of tPA among the medical experts who treated strokes patients at the time. The market for tPA appeared to be structured similarly in the sense that a relatively small population of cardiologists were clustered around certain medical centers in the US and the company could directly reach out those medical centers through a small sales and marketing operation. Despite the relatively small size of this market, the product could become a blockbuster considering that such a product with no competitor was priced at over $2,000 in the late 1980s and no real competitor was expected to enter the market, given the difficulties of matching Genentech's high quality (Pollack 1990; Goeddel 2003).

During the 1980s Genentech pursued various different product development initiatives through in-house research or joint ventures. Innovation efforts were sustained through a period in which raising large amounts of capital wasn't an easy matter. After the changes in the R&D tax credits, raising capital through such funds was no longer an option. A follow-on stock offering wouldn't be feasible, given the market conditions in the late 1980s. As the size of the operations and workforce grew so did the operation costs. The sales of tPA, the company's flagship product, had failed to meet market expectations in the late 1980s due to the high price tag associated with the product (Pollack 1990).

For a hands-on manager such as Swanson managing the affairs at Genentech ultimately became a difficult matter, given the growing disappointments with share prices, innovation productivity, sales performance, etc. As a response to declining operational performance, Perkins, the chairman of the board, and Swanson, the CEO, decided to recruit a seasoned executive to help management. Former CEO of Abbott, Kirk Raab, was chosen to be the right candidate to support Swanson in operational affairs (Perkins 2002).

The declining stock prices were especially troubling for the company, given that the company stocks had been used as a currency when the company was short of cash. Aside from the collateral function to raise funds for financing clinical trials, stocks served as a speculative currency to attract and retain some of the most talented scientists in molecular biology who were in short supply in the late 1970s and early 1980s. Middleton (2002) gives the most credit to himself on the innovative use of *junior common stocks* for the effective management of workforce and organization-wide motivational alignment.

Highly qualified candidates, who are most likely to have a stable employment at a university or big pharma, can only be attracted to working for a start-up by allowing the individual to purchase the founders' stock, a type of stock issued to founders when the company was formed, at a price that is significantly below the price of the company's common stock. Once the start-up company goes public those with the founders' shares have the incentive to remain employed given the value of such stock can only appreciate more (Middleton 2002). If not, liquidity now exists for the stock to trade easily on the stock market.

The real challenge for Genentech was to find a way to manage the price risk for the stocks following the IPO event. Because the PLIPO status remains in the post-IPO period, stock prices could be volatile at times, and some sharp moves in stock prices could be observed when some negative news might or might not have involved the company. These risk factors associated with a PLIPO such as Genentech could deter top candidates from taking jobs at PLIPOs, given that there would always be another early stage start-up that would offer some founder's stock with much greater chance to generate higher return especially at the time of the IPO. By offering *junior common stocks* (also called *earnings convertible* or *restricted stocks*) to employees at discounted rates (calculated at any given time based on some probabilistic calculations)

Genentech had addressed a significant business risk associated with the increasing flow of labor along with the number of new start-ups that were entering the competition (Swanson 2001, Middleton 2002).

As seen in the case of the very first biotech PLIPO, Genentech, a stock can serve various functions and create different classes of shareholders with different sub-identities (i.e. employee-shareholder, scientists-shareholder, VC-shareholder, founder-shareholder, etc.) within the organization. As long as achieving a scientific goal (i.e. first company to clone a gene or bring the first recombinant product to market to cure a disease no other therapies existed before, etc.) remained as the primary motivation of most employees, stock-price performance hadn't done much damage to organizational integration at Genentech.

But once the main motivator was replaced with (or represented in) stock-based performance indicators (earning per share or shareholder value), meeting such goals wasn't as effective as the earlier goals that had driven some of those competitive scientist-shareholders. Excessive dilution of stocks and plummeting prices also made it difficult for Genentech to raise more capital through equity sales (Middleton 2002). Despite its strong pipeline the company had failed to sustain its financial commitment to maintain its learning efforts. The declining share prices in the late 1980s were seen as foregone conclusions resulting from various different strategic miscalculations, and such a trend was considered irreversible by many observers.

The new managerial perspective developed during the crises only increased the division among different classes of shareholders (i.e. many board members had been gathered around the Raab-camp while some core employees gathered around Swanson). This division would ultimately contribute to further decline in the clarity of corporate vision. Exercising strategic control over resource allocation is highly difficult if the leadership cannot motivate enough people to commit to complying with strategic objectives and engaging in the actions plans within an organization that has disintegrated into too many shareholder-camps singing different tunes.

> ***…It is good to have a rich uncle in America. Genentech had a rich uncle in Switzerland****.*
>
> Steve Krognes, Head of mergers and acquisitions, Roche[2]

At the time Genentech was underperforming financially, the company still had a strong product pipeline. It was disappointing to let the very strong pipeline of innovative products go but the board members knew that the current state of corporate finances and the stock performance was something it could not be fixed without outside help. The company had to find a "rich uncle" to help to push the pipeline out to explore the opportunities in global markets (Baldwin 2010). During an interview in 2001 Tom Perkins shared a story to illustrate the shareholder frustration with the market performance and how the company was derailed under the close watch of the legendary business leader of Hewlett Packard, David Packard, who was a member of the board at the tine:

> *I remember the meeting we had with the shareholders where we presented all of this [disappointing market performance that required the board approval for the company's sale to Roche]. One lady stood up and said, "I have a question only for David Packard [given that he was perceived to be a mentor for both Perkins and Swanson]. How could you permit this to happen Mr. Packard? It's like leaving New York on a train to San Francisco, and you're making us get off in Denver. How could you permit this?" His answer was, basically, "I'm doing what I*

[2] Such statement of Krognes summarizes the nature of relationship between Roche and Genentech during the period followed by acquisition as cited in Baldwin (2010).

was told." [laughter] He didn't use those words, of course. But she was so disappointed. We all were. It wasn't a happy thing. But we all felt that we had to do it (to approve the acquisition deal]. The loss of independence. It's still an independent company, more or less. It's still a public company, at least. But it's no longer the baby Jesus.

Even Roche had been aware of the scale of financialization that had taken place within a once upon a time innovative organization that had managed valuable assets but had run out of gas before the next pit stop to refuel. It was a general consensus among the people at Genentech that Roche was the most appropriate candidate to acquire such a valuable pipeline (Goeddel 2003, Perkins 2002).

The case on Roche's transition to molecular genetics mostly explains the basis for this consensus: strong cultural appreciation and commitment to the underlying science Roche had possessed at the time of acquisition. Roche managers were also smart enough to evaluate the situation correctly and came up with the right approach to acquire a company without losing the most important thing that had made the company highly innovative: human and intellectual assets. They also knew what was not needed in this equation, and hence, eliminated them: too many shares and holders! Solutions? Since the employee motivation had been extensively tied to the company's stock, let the shares continue to float in the market; since Genentech had been an organization overly proud of independent spirit, let the company own the other half of itself. After all 51% is all it takes to run a company efficiently as the descendants of Hoffmann-Oeri family have been doing it for over a century!

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APPENDICES

Figure 1a: Revenues, by country of product origin (all companies)

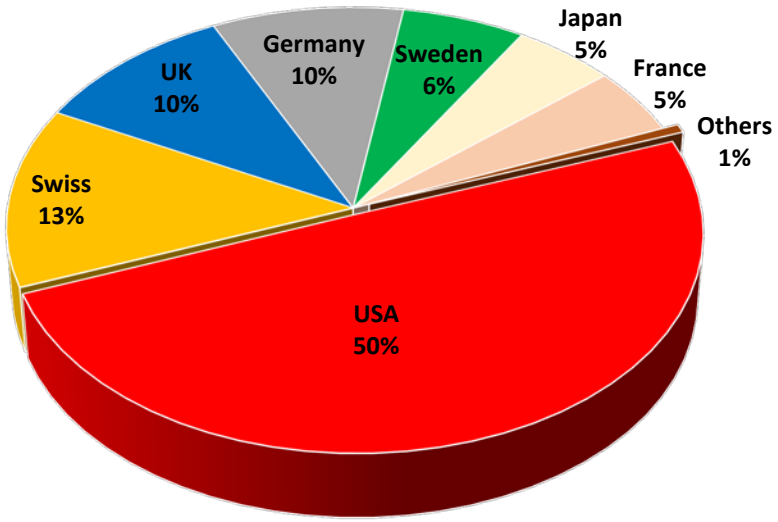


Figure 1b: Number of products in portfolio, by country of origin

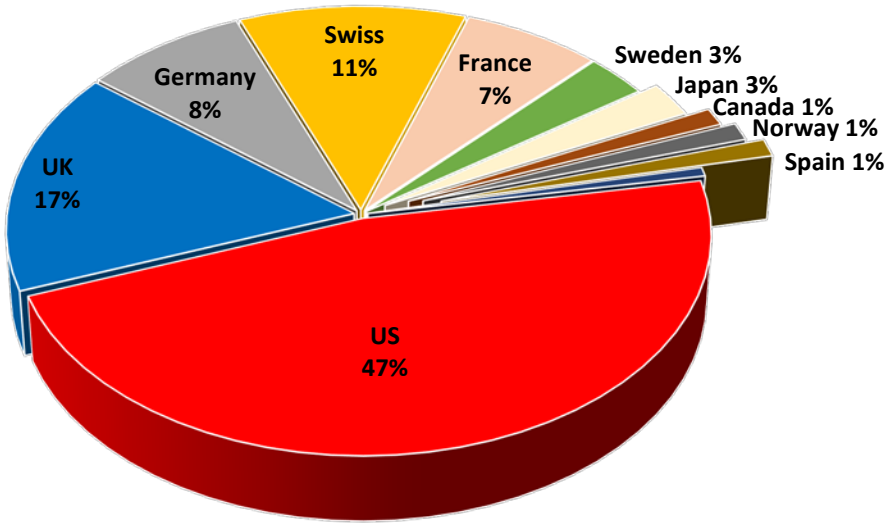


Figure 2: Total revenues, by country of product origin and decades in products launched

Figure 2a: Products launched in the 1980s

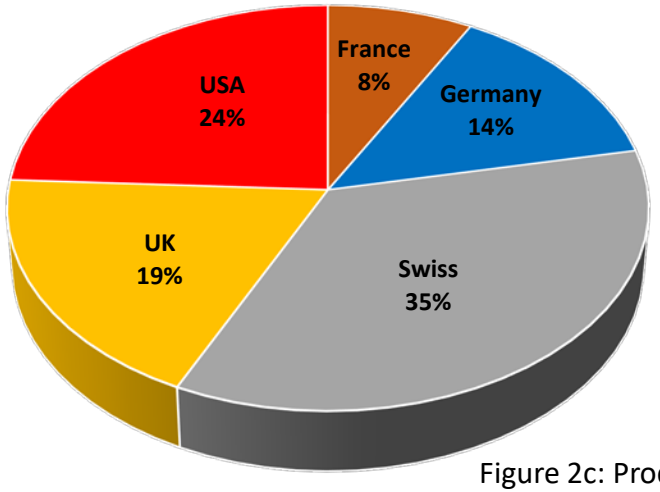


Figure 2c: Products launched in the 1990s

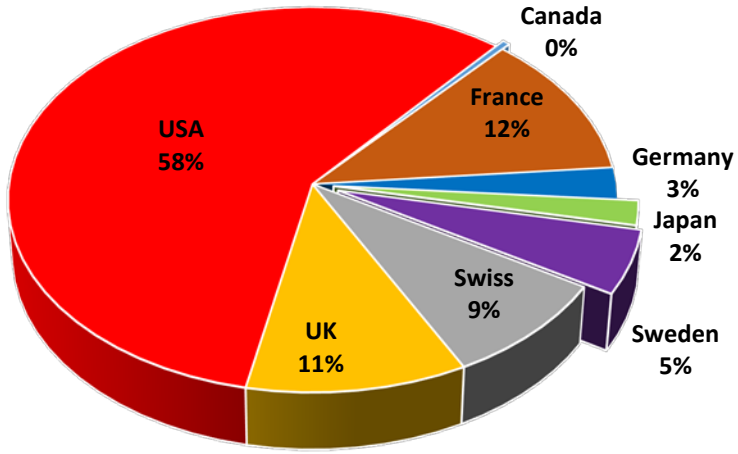


Figure 2c: Products launched in the 2000s

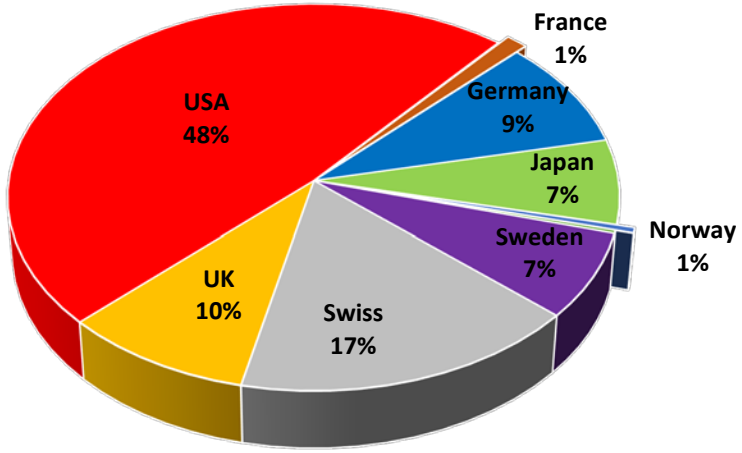
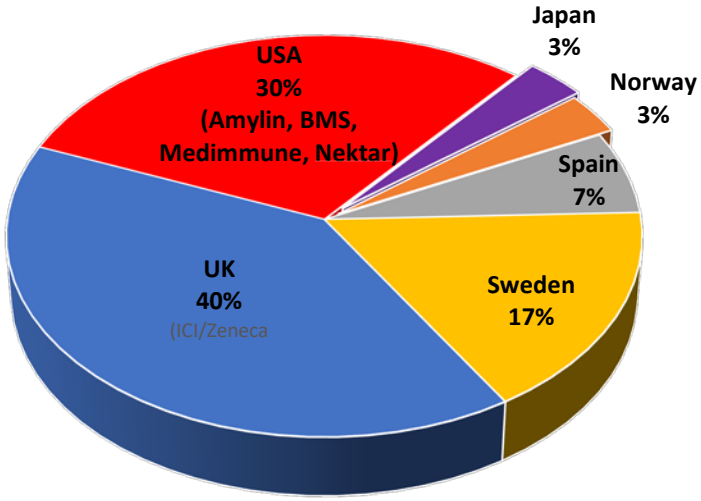


Figure 3: Astra Zeneca (AZ)

3a: Number of products (by country of origin, n=30)



3b: Revenues by country of product origin (Sum=GBP 33.2 bn)

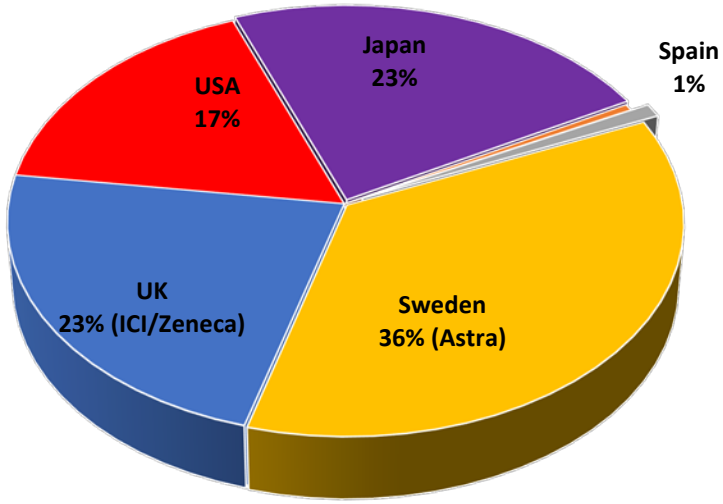
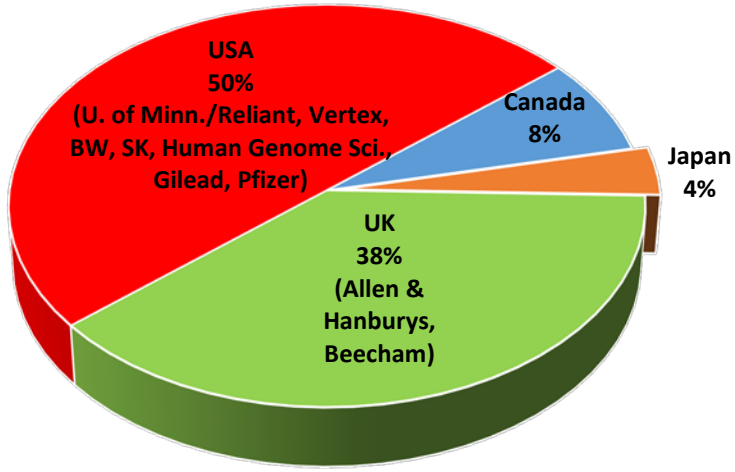


Figure 4: GlaxoSmithKline (GSK)

4a: Number of products (by country of origin, n=26)



4b: Revenues by country of product origin (Sum= GBP 10.8 bn)

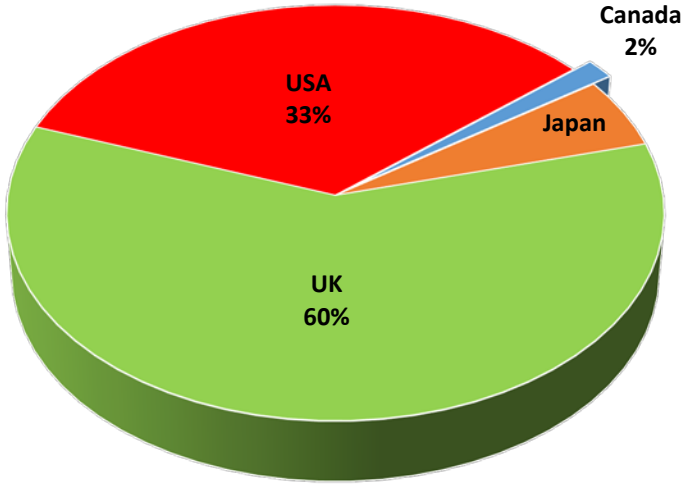
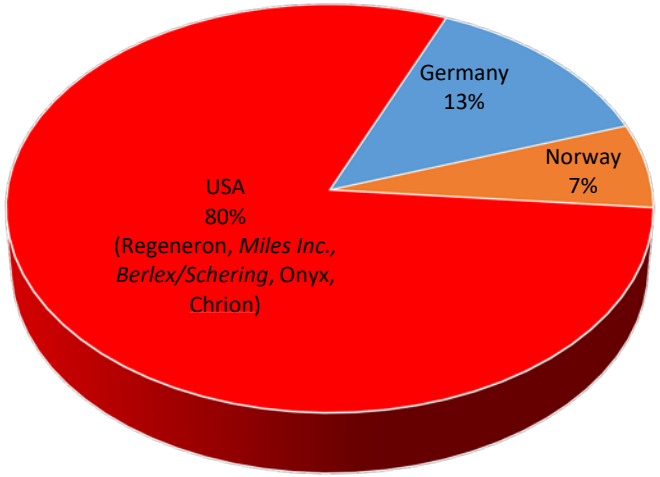


Figure 5: Bayer

5a: Number of Products (by country of origin, n=15)



5b: Revenues by country of product origin (Sum= EUR11.2 bn)

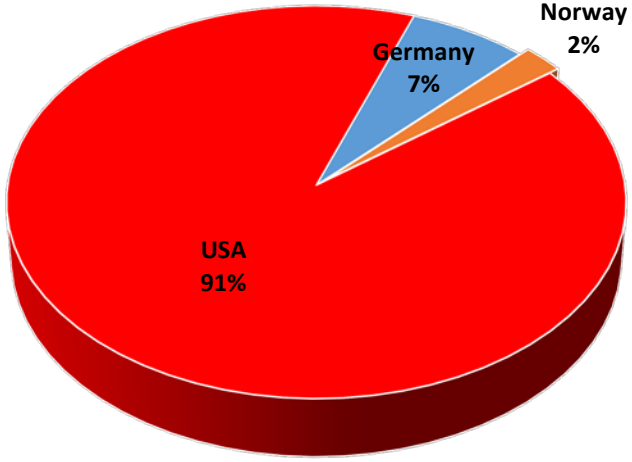
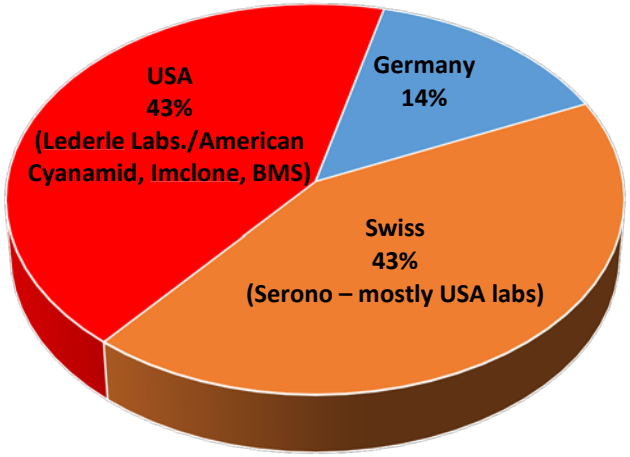


Figure 6: Merck KGaA (Merk-Serono)

6a: Number of Products (by country of origin, n=7)



6b: Revenues by country of product origin (Sum= EUR4.9 bn)

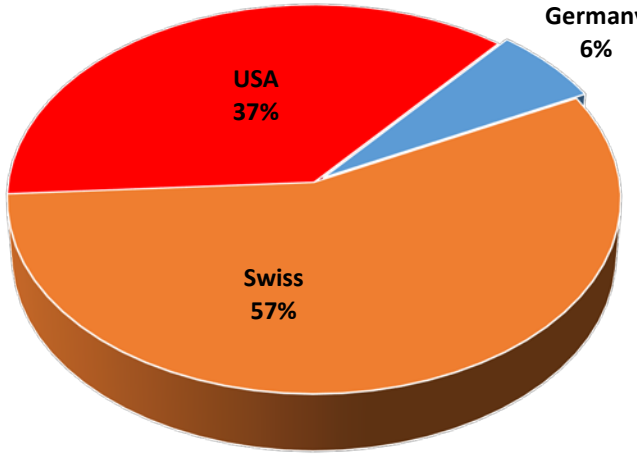
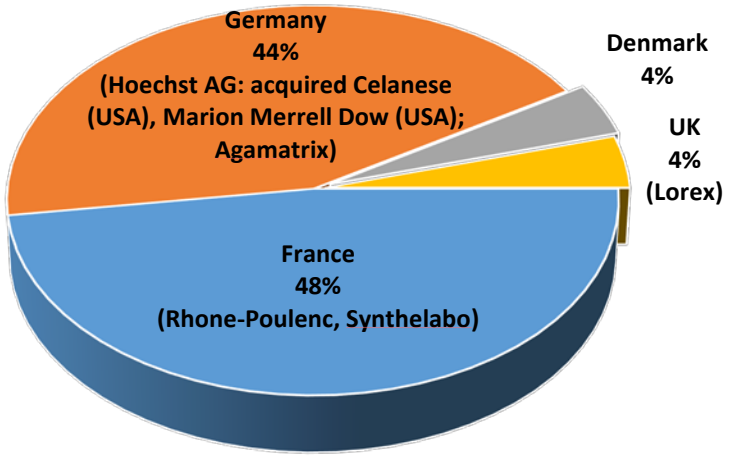


Figure 7: Sanofi-Aventis

7a: Number of products (by country of origin, n=38)



7b: Revenues by country of product origin (Sum= EUR20.2 bn)

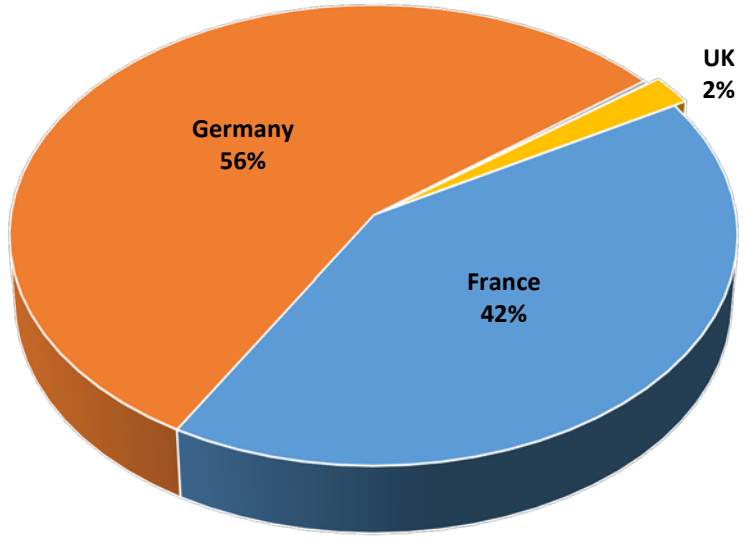
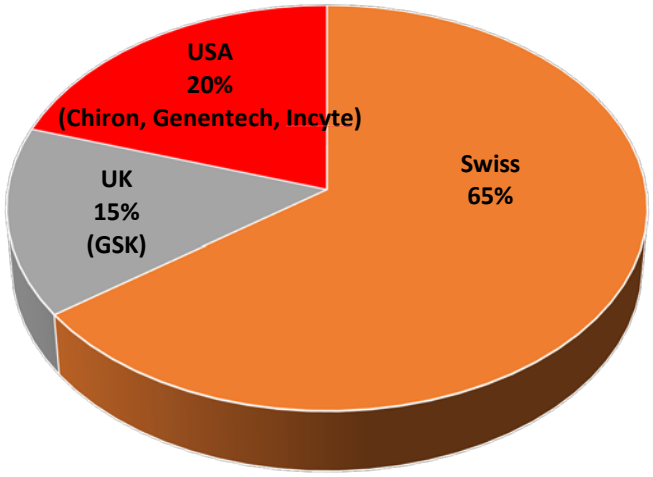


Figure 8: Novartis

8a: Number of products (by country of origin, n=20)



8b: Revenues by country of product origin (Sum=CHF 24 bn)

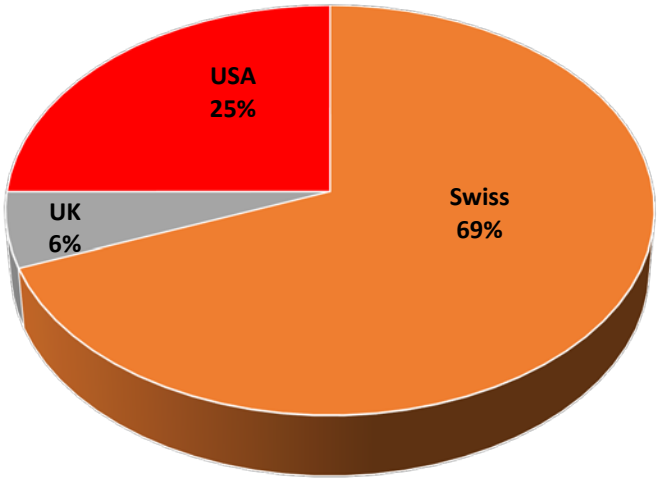
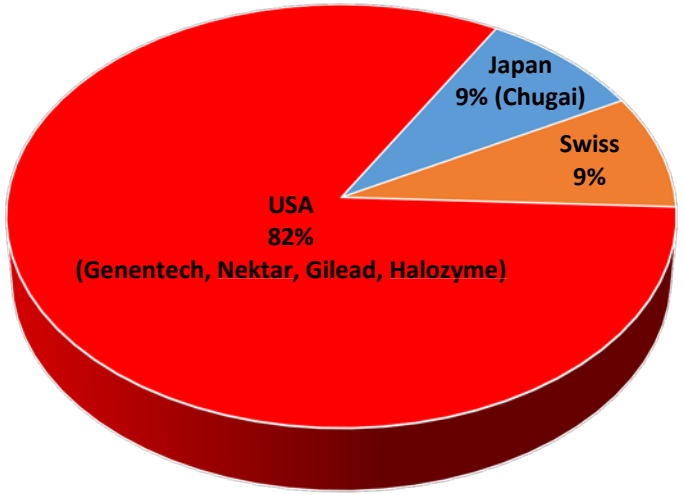


Figure 9: Hoffmann-La Roche

9a: Number of Products (by country of origin, n=23)



9b: Revenues by country of product origin (Sum= CFH 34.8 bn)

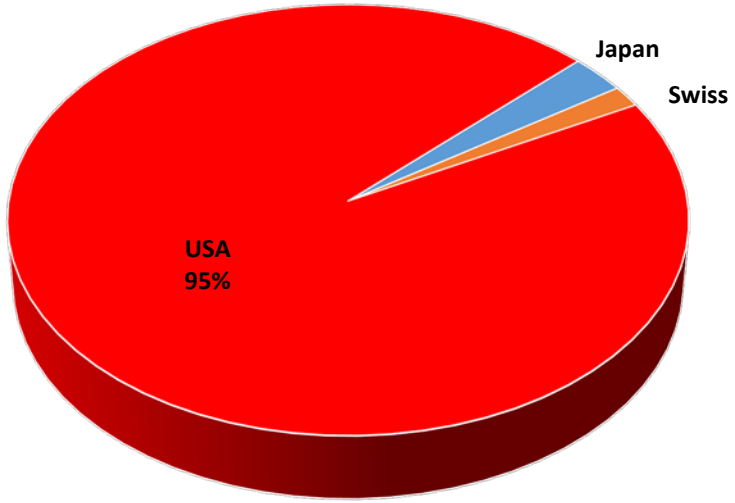


Figure 10: Product candidates in pipeline, by clinical phase

Figure 10a: Candidates in phase I

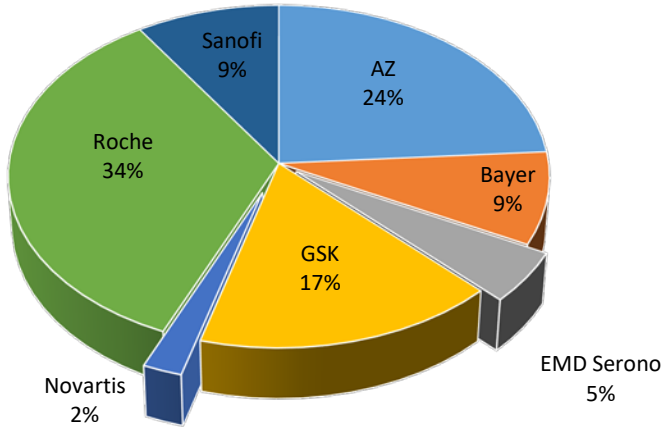


Figure 10b: candidates in phase II

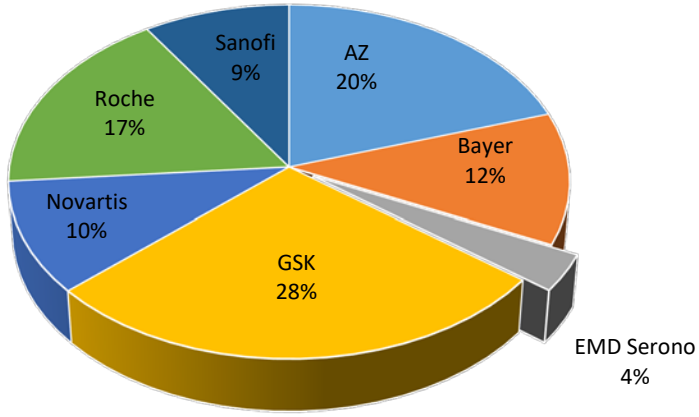


Figure 10c: Candidates in phase III

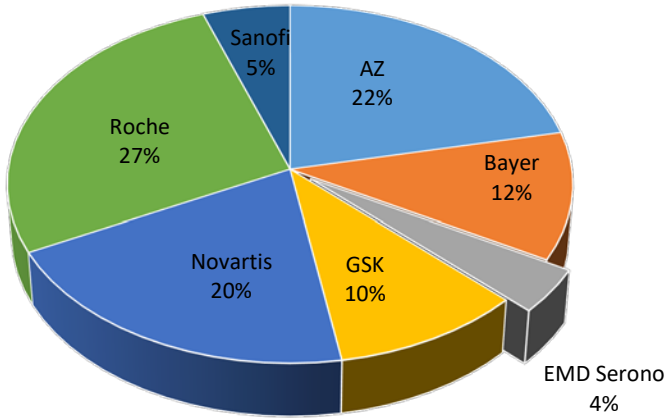


Figure 10d: Candidates in submission for approval