III. SPECIFICITIES IN PHARMACEUTICALS AND RECENT DEVELOPMENTS

A. Innovating and inventing in pharmaceutical industry

While the cumulative development of knowedge and path of innovation may still be the same, each industry has different and specific characteristics. These characteristics include the ease with which inventions can be imitated, the need for cumulative innovation rather than stand-alone development, the speed and cost of R&D. The extent to which patents cover an entire product or a mere component thereof, are all dependent on the industry.[211] The pharmaceutical industry has attracted attention among regulators and policy makers, because it is one of the most profitable and innovative industries and because its products are directly connected to public health. This chapter will explore the specific factors that distinguish the process of R&D and innovation in the pharmaceutical industry from that of other technological industries.

1. Specificities in the drug development process

a) Highly regulated industry

Few industries bear such high regulatory burdens on initial innovations as the pharmaceutical industry.[212] Without regulatory approval, any exclusivity is worthless since the product cannot be marketed. [213] The mission of the drug regulatory authority is to ensure that drugs marketed in a country are safe and effective. To do so, they review the evidence produced and submitted by the companies that seek to market drugs. This rigor on the part of regulatory authorities intensified in the aftermath of scares such as the adul-

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211 *Burk/Lemley*, 89 Va. L. Rev. 1575, 1577 (2003).

212 *Bessen/Meurer,* 2008, 89; *Roin*, 87 Tex. L. Rev. 503, 516 (2009) (raising examples such as agricultural-chemicals and medical-equipment industries which are governed by regulatory regimes.).

213 *Teece*, 15 Res. Policy 285, 300 (1986).

terated sulfamilamide case in the United States and regulation became even more stringent following the thalidomide tragedy in the late 1950s and early 1960s.[214] The Vioxx®' withdrawal in 2004 was one of the most recent events that alarmed authorities.[215]

In order to ensure the safety of the public, it is right and proper that drugs be thoroughly tested and that information regarding safety and efficacy be produced before the drugs are marketed. This demanding requirement, however, typically leads to prolonged preclinical and clinical trials.[216] Moreover, the regulation has become ever more stringent over time.[217]

b) R&D – a costly and lengthy road to a medicine

The process of developing a drug typically is sequential. First, a compound is identified which may have promising therapeutic efficacy throughout lead compound identification and repeated chemical optimizations in the laboratory. Next, the selected compound must pass preclinical testing in vitro and in animals, a new drug application must be filed with the administrative authority, three phases of clinical trials in humans must be completed,[218] and

214 *Scherer*, 2007, 22; *William*, 1999, 87 (noting after the prescription of thalidomide for pregnant women to treat morning sickness, it was found that thalidomide was responsible for the fetal defects, and that one of enantiomers was responsible for the beneficial effect and the other was for the side effect.); *Mann/Andrews*, 2007, 3 (also mentioning after this thalidomide disaster, drug regulatory mechanisms of today had been established).

215 *Horton*, 364 Lancet 1995, 1995 (2004).

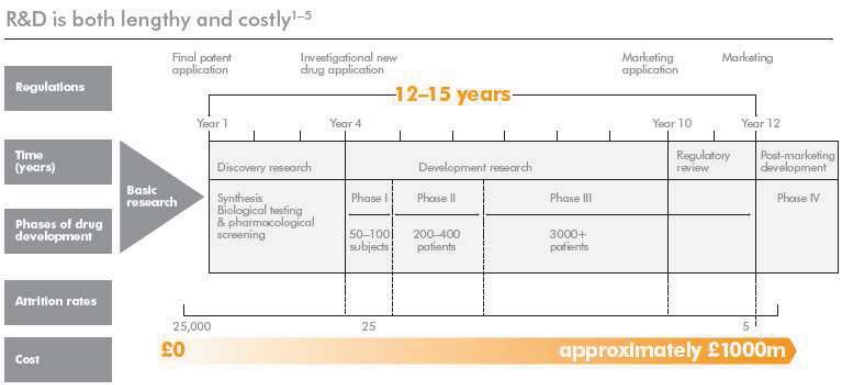
216 Clinical development accounts for around 63% of the costs for developing each NME, and 53% of the costs are incurred from Phase II to launch. *See e.g., Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 205 (2010).

217 *Dutfield*, 2009, 295-96; *Federsel*, 18 Bioorgan. Med. Chem. 5775, 5777 (2010).

218 Phase I trial is performed on a small number of (usually) healthy volunteers to obtain information on toxicity and safe dosage ranges in human. In phase II trial, the drug is administered to a large number of individuals who were selected from the patients for whom the drug is intended to be beneficial. In final phase III trial, many patients are enrolled and it is tried to detect adverse reactions which less frequently occur in patient populations. During these clinical trial phases, extensive toxicology experimentations on animals, long term stability testing, additional dosage formulation work, process development to supply enough compounds for the clinical testing also often occur in parallel. *See e.g., DiMasi/Hansen/Grabowski*, 10 J. Health. Econ. 107, 110 (1991); *See e.g., Scherer*, 2007, 5-8.

a drug must survive a final administrative authority's review.[219] The considerable increase in the duration of clinical and pre-clinical studies is due to an escalation in the obligatory numbers of subjects for the clinical trials,[220] the increased requirement of mandatory analytic, pharmacologic, toxicological, and clinical trials,[221] and the increased number of studies on the treatment of chronic conditions, such as cancers, immunological disorders,[222] and cognitive disorders. This whole process currently takes 10 to 13 years, significantly longer than it was 40 years ago, when the average period was 8 years.[223] Figure 3 shows a recent example.

Figure 3: R&D, a long and costly process[224]



1. Vernon JA, Golec JH, Dimasi JA. Drug development costs when financial risk is measured using the Fama-French three-factor model. Health Economics 2009 doi: 10.1002/hec.1538.
2. Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2008 (Washington, DC: PhRMA, March 2008).
3. Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2008.
4. ABPI data on file.
5. Paul S, et al. Nature Reviews 2010; 9:203–214.

219 *See generally, DiMasi/Hansen/Grabowski*, 10 J. Health. Econ. 107, 109-11 (1991); *Schuster/Laggner/ Langer*, 11 Current Pharmaceutical Design 3545, 3545 (2005).
220 *DiMasi/Hansen/Grabowski,* 22 J. Health Econ. 151, 177 (2003).
221 *Brandt*, 1996, 129; *Dickson/Gagnon*, 3 Nat. Rev. Drug Discov. 417, 420 (2004) (e.g.: more extensive regulatory requirements to mandate to include women and children in the test).
222 *Dickson/Gagnon*, 3 Nat. Rev. Drug Discov. 417, 420 (2004).
223 Dickson/Gagnon, 4 Discov. Med. 172 (2004); *see also EFPIA*, 2012, 6 (reporting 10 years of R&D period and 2~3 years of administrative procedure); *Grabowski/ Kyle*, 2008, 275 (noting the R&D process of a medication from the synthesis of a compound synthesis to marketing approval of it typically takes more than a decade.).
224 *Association of the British Pharmaceutical Industry ("ABPI")*, 2011, 10.

The process is of course costly.[225] However, just because something is expensive does not mean that it is good, and there is no reason that the cost should be maintained at this level. In this respect, the figures sometimes speak for themselves. Though the process of estimating the cost of NMEs largely varies by therapeutic indications and is complicated, since the money spent on R&D is regained in revenue over several years, studies have shown a dramatic increase in cost. The average cost of preclinical and clinical studies for traditional products (small chemicals) was estimated at 0.8 billion USDs in 2000,[226] which was double the cost of the previous fifteen years.[227] An updated estimate of the same type of products was 1.3 billion USD in 2010.[228] The introduction of new drugs to the market is financed almost entirely by the private sector, even though the result of investment is regarded as a public benefit.[229] Some scholars have argued that the initial stages of high risk projects could be subsidized by government, since basic research projects often involve high costs and potentially high but uncertain rewards.[230] A contrasting example is the computer industry, where two pro-

225 *ABPI*, 2011, 10; *Schuster/Laggner/ Langer*, 11 Current Pharmaceutical Design 3545, 3545 (2005); cf. *Cockburn*, 2006, 13, 25 (noting the trend of increasing R&D expenditure was "to some degree" overstated however admitting the growth in R&D spending was "substantial.").

226 *DiMasi/Hansen/Grabowski,* 22 J. Health Econ. 151, 166-67 (2003).

227 *Anonymous*, 418 Nature 353 (2002).

228 *Federsel*, 18 Bioorgan. Med. Chem. 5775, 5777 (2010), in 2009, the average cost of R&D to bring an NME to the market by large pharmaceutical companies is estimated to be up to around 1.8 billion USD. *See Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 204 (2010); *See also O'Hagan/Farkas,* Bain Insights [online] 1 (2009) (noting "Bain's drug-economics model shows that the situation is untenable. In the late 1990s, pharma companies spent $1.1 billion, on average, to develop and launch a new drug. Today, just a decade later, the investment has doubled to $2.2 billion."); Recently Forbes even has reported the average drug developed by major pharmaceutical companies costs at least 4 billion USDs and could come to 11 billion dollar, *see Herper*, Forbes, February 2, 2012 (introducing Eli Lilly's average cost of bringing a new drug to market is 1.3 billion USDs which is the price that would buy 371 Super Bowl ads, 16 million official NFL footballs, two pro football stadiums, pay of almost all NFL football players, and every seat in every NFL stadium for six weeks in a row).

229 *Dickson/Gagnon*, 3 Nat. Rev. Drug Discov. 417, 427 (2004); s*ee also Tuominen*, 2011, 4; *see also U.S. Department of Commerce International Trade Administration,* 2004, vii.

230 *Merges*, 7 High Tech. L. J. 1, 47 (1992); *Nelson*, 2000, 98.

grammers could develop a commercial software program in a garage.[231] Even though the cost of writing code for operating systems has increased, this takes considerably less time and is cheaper than developing a new drug.

Even the figures given above may represent an underestimate of the real costs of drug discovery.[232] Significantly, the figures do not include costs incurred prior to the target validation.[233] The research required to identify and validate a given target varies by subject, which makes the underlying parameters difficult to quantify.[234] Most importantly, these figures do not include the R&D costs for products that cannot be launched on the market,[235] which is the main expense in the industry. It has been reported that 75% of the fully capitalized cost of developing a new medication is the average cost of failures.[236] As Jacob LJ puts it simply: "*The few winners must pay for all the losers.*"[237] These failures are also based on uncertainty in developing a drug.

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231 *Burk/Lemley*, 89 Va. L. Rev. 1575, 1582 (2003) (e.g. Steve Jobs and Steve Wozniak for Apple Computer; Bill Hewllet and David Packard for Hewlett-Packard started in a garage).

232 Some scholars also argued expenditure for marketing support or cost for post-market surveillances, line extensions, development of new indications, and the development of new formulations, dosage forms and so on must be added., *see Fedorsel*, 18 Bioorgan. Med. Chem. 5775, 5777 (2010); *see Munos*, 8 Nat. Rev. Drug Discov. 959, 962-63 (2009); *See also Pisano*, 2006, 120.
However, these are mainly not the cost to bring a NME to the market, thus it would not be proper to include them.

233 *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 205 (2010); In the drug discovery, a "target" can mean a target protein which plays key role in the function of normal and abnormal cells, which leads to the formation of hypothesis that the modulating the function of this protein which linked to disease could be a route to a new medication. This kind of disease-linked protein is referred to as a target, and the process of confirming such hypothesis is usually referred as "target validation." *See Knowles/Gromo*, 2 Nat. Rev. Drug Discov. 63, 63 (2003).

234 *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 205 (2010).

235 *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 205 (2010).

236 *Cockburn*, 2006, 17.

237 *Jacob*, December, CIPA 711 (2008).

c) Uncertainties in post-invention development

"*A hallmark of medical decision-making is choice under uncertainty*."[238] "*[D]rug development remains part science and part art.*"[239] These statements reflect the uncertainty of even post-invention development in this field. At least three levels of risk are are derivable from scientific, regulatory, and economic uncertainty respectively.[240]

(1) Scientific uncertainty: Unpredictability of substances

Firstly, scientific uncertainty arises because of the unpredictability of substances. Owing to this unpredictability, only one of every 10,000 new substances reaches market approval.[241] It is well established that the properties of chemical compounds are substantially contingent upon their chemical structures. However, it is no longer disputed that a small structural modification may result in major differences in biological activity,[242] which is to say, reasonable predictions of relations between structure and activity can be found in general with some limit beyond which no such prediction can be validly made.[243] This unpredictability is also clearly demonstrated by the reasoning of the courts, which require higher disclosure in this field than in other technological fields.[244] In other words, since there is less room for the

238 *Frank*, 2004, 9.
239 *Bartfai/Lees*, 2006, 258.
240 *Dickson/Gagnon*, 3 Nat. Rev. Drug Discov. 417, 419-420 (2004).
241 *Hansen/Hirsch*, 1997, 326; *ABPI*, 2011, 10 (reporting pharmaceutical industry has an attrition rate of NMEs, from discovery to product, of 25,000:5); *see also Heilman*, 4 Quality Assurance, 75, 75 (1995); *see also EFPIA*, 2012, 6 (reporting one or two out of every 10,000 substances may successfully become marketable medicines); *see also Kola/Landis*, 3 Nat. Rev. Drug Discov. 711, 712 (2004) (reporting 62 percent of drug candidates that made it through Phase I failed to pass Phase II, and 45percent of those that did fail to pass Phase III); *see also* Figure 3.
242 *Agrevo/Triazoles*, T 939/92, OJ EPO 309, 325 (1996), point 2.6.2.
243 *Agrevo/Triazoles*, T 939/92, OJ EPO 309, 325 (1996), point 2.6.2.; *see also Ciba-Geigy/Benzothiopyran derivatives*, T 20/83, OJ EPO 1983, 419, 421 (noting "[a]s a rule, prediction by persons skilled in the art is no longer possible where the substances whose properties have to be assessed have been theoretically synthesized, by interchanging all the structural elements from compounds forming the state of the art and having the same kind of effect. Such is the case in this instance.").
244 *Brandi-Dohrn*, Gewerblicher Rechtsschutz und Urheberrecht Internationaler Teil ("GRUR Int") 1995, 541, 543; *see also infra* 899.

person skilled in the art to be able to know possession of an invention, more variants need to be enabled to meet the disclosure requirement in the pharmaceutical art. Thus, when many compounds are disclosed in the prior art, it would be unreasonable to expect that these compounds would exhibit similar technological effects to those shown by substances for which practical data are provided.[245]

(2) Regulatory and market uncertainties

During the long period of acquiring regulatory approval, the high probability of failure in each clinical trial phase and thus failing to acquire regulatory approval risks the business in this sector.[246] Many failures occur in the later stages of development such as during clinical trials.[247] Indeed, 78% of NMEs that survive all of the phases of clinical trials are never marketed.[248] Across the entire process of the product development path, therefore, pharmaceutical companies need to review the status of development and make a so-called "Go/No-Go" decision, namely, a decision about whether to continue to develop or not at several points until the final decision to launch the end product.[249]

Even after a launch, there are some uncertainties in the market environment, such as the acceptance of a new medical product not only by the patient but also by physicians who show a high degree of loyalty to familiar medications.[250] Furthermore, information generated by the pharmaceutical companies after the launch can indicate that the drugs are unsafe or not sufficiently effective.[251] This information can cause sales to plummet,[252] or cause

245 *Brown*, 31 J. Chem. Inf. Comp. Sci. 2, 3-4 (1991).
246 *Dickson/Gagnon*, 3 Nat. Rev. Drug Discov. 417, 419-420 (2004).
247 *Cockburn*, 2006, 17-18.
248 *Frank*, 22 J. Health Econ. 325, 327 (2003); *DiMasi/Hansen/Grabowski*, 22 J. Health Econ. 151, 165 (2003).
249 *DiMasi/Hansen/Grabowski*, 10 J. Health. Econ. 107, 109 (1991) (noting these decisions would be dependent upon potential therapeutic efficacies, frequency and severity of adverse drug reactions, marketing, distributing, productions costs, patent protectability, and the like.).
250 *Dickson/Gagnon*, 3 Nat. Rev. Drug Discov. 417, 419-420 (2004).
251 *Eisenberg*, 5 Yale J. Health Pol'y L. & Ethics 717, 718 (2005); this is also partly because that some side effects can be only found after disclosing the medication to a larger population than that of clinical trials.
252 *Eisenberg*, 5 Yale J. Health Pol'y L. & Ethics 717, 718 (2005).

the product to be removed from the market.[253] The most famous case in point is Vioxx®, which revealed a serious adverse cardiovascular effect after FDA approval.[254] This caused Merck to remove the product from the market and resulted in a catastrophic loss of value, including high litigation costs thereafter.[255]

d) Information rich chemicals

Information is, by nature, expensive to produce, cheap to reproduce, and difficult to profit from.[256] Unlike other chemicals, such as organic solvents, drugs are information-rich chemicals. This is partially because regulation demands production and disclosure of the huge amount of information that is necessary to meet the regulatory authorities' standards must be accumulated and disclosed.[257] This information concerning the use of chemicals is expensive to produce as discussed in chapter III.A.1.b). Once produced and disclosed, however, it is easy to reproduce and difficult to keep exclusive. Risks surrounding the information and its non-excludability further contribute to the uncertainty of the drug development process.

253 *Schuster/Laggner/ Langer*, 11 Current Pharmaceutical Design 3545 (2005) (noting "[o]ver 90% of the market withdrawals were caused by drug toxicity.").

254 *Bresalier, et al*, 352 New Eng. J. Med. 1092, 1098 (2005).

255 Litigation costs were 4.85 billion USDs funding to the expected settlement to resolve roughly 50,000 lawsuits in 2007, or 58 million USDs to settle allegations advertising Vioxx® with 30 US states in 2008. *See Martinez, et al.,* Wall St. J., Oct. 1, 2004, at A1; *see also Merck*, Merck Press Release, Nov. 9, 2007.

256 *Nordhaus*, 1969, 70.

257 *Eisenberg*, 5 Yale J. Health Pol'y L. & Ethics 717, 717 (2005); see also *DiMasi/ Hansen/Grabowski,* 22 J. Health Econ. 151, 166 (2003) (estimates average costs to develop a new drug at $802 million in 2003); *Burk/Lemley*, 54 Case W. Res. L. Rev. 691, 726-728 (2003); creating the information can be risky considering some information generated during or after the R&D procedure of a drug can make the medication withdrawn from the market.

2. Specificities in the market for pharmaceuticals

a) Imitation with negligible cost and much reduced risk

Imitation is a typical example of information spillover.[258] The risk of imitation, of course, haunts all investments in any field of R&D.[259] Imitation follows closely and only on the heels of successful innovation.[260] The innovator's R&D returns can be maximized by an intermediate delay between his own invention and the successful imitation thereof.[261]

The relative ease of imitation with or without patent protection is one of the main factors that differentiates the pharmaceutical industry from others.[262] Sherer takes the aircraft industry as an example, which also utilizes sophisticated technology and spends billions of dollars to develop new products.[263] Even without patent protection, however, in attempting to imitate anAirbus A380, a firm would spend nearly as much as Airbus did to develop its own A380. Moreover, by the time the imitator had completed its rival A380, Airbus would be a decade ahead in sales and would enjoy a substantial production cost advantage. The software industry is another example. Even after a product embracing the invention is available on the market, reverse engineering is both difficult and time consuming.[264]

In contrast, in the pharmaceutical industry, much R&D is directed to securing information,[265] and, once the required knowledge is accumulated, if there is no protection, it *ipso facto* becomes available to any interested party. With such information, it is relatively cheap and quick for an imitator to

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258 *Dasgupta*, 98 Econ. J. 66, 74 (1988).

259 *Jaffe/Lerner*, 2004, 41; *cf. Bessen/Maskin*, 1999, 2 (noting, however, for industries like software and semiconductors, imitation promotes innovation and long patents of broad scope would inhibit it, because the innovation in these industries are both sequential and complementary.).

260 *Cadot/Lippman*, 1995, 1; *see also Christie, et al*, 8 PLoS Med 1 (2013) (In addition to these imitating activities, there are patenting activities by the companies other than the drug's originator to seek monopoly control over innovations to blockbusters).

261 *Cadot/Lippman*, 1995, 15-17.

262 *Scherer*, 2007, 33-34.

263 *Scherer*, 2007, 33-34.

264 Johnson-Laird, 19 U. Dayton L. Rev. 843, 843-44 (1994); *Burk/Lemley*, 89 Va. L. Rev. 1575, 1584 (2003).

265 See subsection III.A.1.

identify the composition of a new medication and to manufacture it.[266] In addition, the knowledge of an innovator's success itself reduces the risk of failure for the imitator. The knowledge of success, in other words, reduces a great deal of an imitator's uncertainty,[267] which cannot be compared with that of innovator. Thus, there are few barriers to imitation, without patent protection.[268] This can be clearly observed in the quick and vast market erosion once the patent term of a product expires and generic versions of that product enter the market.[269]

b) Prescription based purchase: A disconnection between choosers and payers

As in other industries, medicines are produced by pharmaceutical companies and consumed by end-users, i.e. patients. However, unlike other consumer products, medicines are often chosen and/or prescribed by medical doctors and normally paid for or reimbursed by insurance companies or the relevant health system.[270] This is especially true of prescription drugs that cannot be sold without a doctor's prescription. Consequently, the person who prescribes the drug, the purchaser, and the end-consumer of the drug may in fact be different in most cases. This disconnection between the person who selects and the person who pays and consumes causes the demand for prescription drugs to be more price-inelastic than that of over-the-counter

266 *Mansfield/Schwartz/Wagner*, 91 Econ. J. 907, 913 (1981); mentioned in *Roin*, 87 Tex. L. Rev. 503, 511 (2009) (noting generic drug manufacturers spend on average about $2 million on the approval process).

267 *Kieff*, 85 Minn. L. Rev. 697, 709 (2001).

268 *Teece*, 15 Res. Policy 285, 300 (1986); *Roin*, 87 Tex. L. Rev. 503, 516 (2009) (raising examples such as agricultural-chemicals and medical-equipment industries which are governed by regulatory regimes.).

269 The asymmetry between pharmaceutical innovators and imitators was not as glaring before the regimes like Hatch-Waxman Act or Regulation on SPC with Bolar exceptions were introduced. Until early 1980s, generic drug providers could have invested nearly as much as the original companies did. *See Scherer*, 2007, 34-35; *see also Bond/Lean*, 1977.

270 *DG Competition*, 2009, 21-22 (see also Figure 2 in page 22).

("OTC") drugs, which may be sold without prescription.[271] In contrast, for prescription drugs, the prescribers do not pay for the drugs that they order.[272] As this disconnection causes prescription drugs to be cost-insensitive, demand curves can be easily manipulated through advertisement and promotion.[273]

c) Information asymmetry and high loyalty to a medicine

Markets for medical care are also characterized by asymmetric information between physician and patient.[274] Patients do not have enough information generally, which leads to fear, anxiety, and reluctance to switch to another version of a medicine.[275] Unwavering loyalty to a particular medicine also induces patients or doctors to stay with the same product.[276] This loyalty makes it difficult not only to leave a familiar product for a new product in the same therapeutic class, but also for a generic version of the same product. Since doctors and patients are accustomed to brand-named products, although available generic substitutes containing exactly the same active ingredients are much cheaper, they remain reluctant to substitute any unknown generic versions for the brand-named drug, even if health authorities guarantee their bioequivalencies.[277] Another contributing factor is that the price changes have a small effect on the quantity of the drug in demand. Some

271 *Temin*, 10 Bell J. Econ. 429, 434-5 (1979) (noting that the customers were changed from patients to doctors who had a peculiar characteristic; "they did not pay for the drugs they ordered. In fact, they did not even know how much these drugs cost."); *Steele*, 5 J. Law Econ. 131, 139-43 (1962) (noting the demand curve for the physicians' were an upward slope, but "the demand curve of the patient is perhaps nearly vertical up to prohibitively high prices if he trusts the judgment of his physician."); *Teece*, 15 Res. Policy 285, 301 (1986) (noting "FDA regulation which had the de facto effect of reducing the elasticity of demand for drug…").

272 *Temin*, 10 Bell J. Econ. 429, 434-35 (1979) (noting that the customers were changed from patients to doctors who had a peculiar characteristic; "they did not pay for the drugs they ordered. In fact, they did not even know how much these drugs cost."); *Steele*, 5 J. Law Econ. 131, 139-43 (1962).

273 *Rai*, Ill. L. Rev. 173, 206 (2001).

274 *Frank*, 2004, 10.

275 *Frank*, 2004, 27-28; *Yu/Gupta*, 2008, 31.

276 *Landes/Posner*, 2003, 190, 313-14; *Grabowski/Vernon*, 35 J. Law Econ. 331, 333-35 (1992).

277 *Landes/Posner*, 2003, 314; *von Hippel*, 1988, 53.

evidence suggests that, even after the expiration of the basic patent term, the price of product covered by the basic patent sometimes does not substantially decrease.[278]

d) Pricing

"*Every day in our lives monopoly takes its toll.*"[279] One may recall the term monopoly from the term patent. Monopoly, however, is a term that relates to a market rather than to any particular good or service sold in that market.[280] While all property rights can be regarded as monopolies, only those that convey effective control over the relevant market can provoke economic inefficiencies associated with monopolies, such as when there are no adequate market alternatives and consumers are consequently willing to pay a monopoly price.[281] In the same vein, patent law does not confer an economic monopoly, but only the right to exclude others from producing products covered by the patent.[282]

Though some scholars argue that there is no competition where patented drugs are concerned,[283] the reality is different. Firstly, the prices of prescription drugs are largely regulated.[284] As Landes and Posner noted, "The evidence is consistent with government regulation that limits the ability of

278 *Grabowski/Vernon*, 35 J. Law Econ. 331, 374 (1992); Even there were evidences that branded-drug prices raised after the patent expiry and generic's entrance; *Berndt*, 16 J. Econ. Perspect. 45, 63 (2002); *Davis/Murphy/Topel*, 2001, 2.

279 *Kefauver*, 1966, 3.

280 *Kieff,* 2008, 21; *Dam,* 23 J. Legal Stud. 247, 249-50 (1994) (noting "it is readily apparent that the right to exclude an-other from "manufacture, use, and sale" may give no significant market power, even when the patent covers a product that is sold in the market. Also "leading companies may obtain 1,000 or more patents in a single year, and yet many such firms are unlikely ever to obtain even a single monopoly in the market"); *Illinois Tool Works Inc. v. Independent Ink, Inc.,* 547 U.S. 28, 46 (2006) ("Congress, the antitrust enforcement agencies, and most economists have all reached the conclusion that a patent does not necessarily confer market power upon the patentee.").

281 *Kieff,* 2008, 21; *Hovenkamp, et al*, 2010, § 4.2.

282 *Hovenkamp, et al*, 2010, § 4.2.

283 *See e.g., Steele*, 5 J. Law Econ. 131, 147 (1962).

284 *Vernon*, Regulation, 22, 22 (2002-2003, Winter) (for example, direct price control, profit control, reference pricing, approval delays, procedural barriers, and reimbursement).

drug manufacturers to charge monopoly prices to certain segments of the population."[285] According to a report about pharmaceutical price controls in Organisation for Economic Co-operation and Development ("OECD") countries, almost all governments rely on some sort of price controls[286] to limit spending on pharmaceuticals, to prevent pharmaceutical companies from charging a market/based price for their products, and to require that they be transparent about the rationale for prices or reimbursement amounts.[287]

The most direct method is to set the sale price and to make sales at any other price illegal, which generally results in lowering prices below what they would have been in a free market.[288] Another method used is to set the reimbursement price of a new drug at levels well below the free market price.[289] Even in Germany, where pharmaceutical companies could have decided the drug price, rendering Germany one of the highest drug price countries in Europe along with the Netherlands and Sweden, new laws took effect in January of 2011, which forced a company to negotiate new drug prices with health insurers after determining whether the new medication had an additional benefit.[290]

Furthermore, getting a better price and reimbursement is no longer enough, and manufacturers must further prove the effectiveness of products in the real world and provide a pharmacoeconomic analysis that includes cost-effectiveness.[291] Thus, it is more difficult to charge high prices. Sec-

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285 *Landes/Posner*, 2003, 315.

286 *U.S. Department of Commerce International Trade Administration*, 2004, vii-viii; *see also Vernon*, Regulation, 22, 22 (2002-2003, Winter); *see also*, *UK Office of Fair Trading*, 2007, 1-2 (UK had broadly two components; *profit controls* which set a maximum level for the profits which a company could earn from the supply from branded drugs to the NHS and *price controls* which provided companies with freedom to set the initial price of new active substances but impose restrictions on subsequent price increase or *cut the price* at the time of scheme renegotiations); In the US, there are no government price controls over private sector purchases, but the government relies on a strong generic pharmaceutical industry to create added competitive pressures. *See*, *Ellery/Hansen*, 2012, 14.

287 *Ellery/Hansen*, 2012, 12-16; *U.S. Department of Commerce International Trade Administration*, 2004, viii.

288 *U.S. Department of Commerce International Trade Administration*, 2004, ix.

289 *U.S. Department of Commerce International Trade Administration*, 2004, ix.

290 *Bohsem*, Süddeutsche Zeitung, January 23, 2012.

291 *Ellery/Hansen*, 2012, 13-14 (noting a drug company used to only need to prove safety, efficacy, and quality to obtain approval and to market a product.).

ondly, therapeutic competition is more common. Once an innovative drug comes onto the market, the market becomes more competitive, since more than one company may be developing compounds with similar mechanisms of action, even though the compounds themselves are different and can be patent protected.[292] Indeed, there are practically always alternative medications on the market for products treating the same disorders, such as headaches,[293] unless the drug is the first in its class, regardless of whether the alternatives are protected by the patent. Thus, a patent in the pharmaceutical industry does not provide protection that will permit a complete or almost complete market.[294]

On the other hand, it is true that patent rights can confer some power in the market, and the anticipation of a price above the marginal cost creates the incentive to engage in research in the first place.[295] In addition, considering the fact that the manufacturing cost of medications is usually low, the public may have to pay higher prices even for a limited amount of time, which is inherent in the patent system. This can be particularly problematic in this industry, given that the product is a medication, which can improve health condition and save lives.[296]

3. Specificities of the patent protection for pharmaceuticals

a) Patent protection for industrial technologies

There is a strong assumption that patents have played and are playing a crucial role in promoting innovation and the growth of industries.[297] However, it is also clear that, in many areas of technology, their role has

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292 *Dickson/Gagnon*, 3 Nat. Rev. Drug Discov. 417, 421-422 (2004); see also subsection II.D.2.

293 *Landes/Posner*, 2003, 314 (noting the manufacturers of differentiated drugs are competing with each other in a market).

294 *Domeij*, 2000, 174.

295 *Hovenkamp, et al*, 2010, § 4.2.

296 *Rai*, Ill. L. Rev. 173, 187-88 (2001).

297 *Luski/Wettstein*, 1 Probl. Perspect. Manage. 31, 31 (2004); *Ann*, 2009, 361; *Crouch*, 16 Geo. Mason L. Rev. 141, 141 (2008); *Graham v. John Deere Co.*, 383 U.S. 1, 9 (1966) ("The patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge."); *Crouch*, 39 Seton Hall L. Rev. 1125, 1134 (2009).

changed.[298] Arguably, patent protection did not seem to be crucial in most industries except the drug industry,[299] where exploitation of the lead time, moving rapidly along the learning curve, use of complementary sales, service capabilities and secrecy are more emphasized than patent exclusivity.[300] For example, the computer software industry can rely on trade secrecy and copyright protection as alternative intellectual property protection to patents.[301] In the semiconductor industry, since semiconductor chips are covered by many different patents[302] and many companies are pursuing the same faster and smaller chips, they can file applications for similar inventions with overlapping claims and face a greater likelihood of infringing others' patents. Thus, patents can be used actively albeit rather defensively to prevent companies from being sued.[303] Along with these two industries, the computer industry has been among the most innovative in recent years in spite of relatively weak patent protections and rapid imitations, partly because these innovations are both very sequential and complementary.[304] In the end, the usual result in these industries is cross-licensing with a modest royalty fee.[305]

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298 *Kash/Kingston*, 28 Sci. & Pub. Pol'y 11, 11 (2001).

299 *Mansfield/Schwartz/Wagner*, 91 Econ. J. 907, 915 (1981); *Levin et al.*, 1987 Brookings Paper on Econ. Activity, 783, 802 (1987) (noting "the three industries in which product patents were viewed as most effective [were] organic chemicals, pesticides, and drugs."); *Cohen/Nelson/Walsh*, 2000, 1-2, 9, 14; *Cadot/Lippman*, 1995, 4 (noting "[a]fter patents, the most important isolating mechanism emanates from lead times or lags."); *Teece*, 15 Res. Policy 285, 287 (1986) (noting "although [patent] do afford considerable protection on new chemical products"). Some survey results have found that large majority of innovations are not patented in certain sectors. *See Arundel/Kabla*, 27 Res. Policy, 127, 138 (1998) (providing examples of such sectors, such as food, tobacco, petroleum refining, basic metals, automobiles, and other transport equipment); *Bessen/Meurer,* 2008, 89.

300 *Bessen/Meurer,* 2008, 89 ; *Levin et al.*, 1987 Brookings Paper on Econ. Activity, 783, 783-84, 816 (1987); *Cohen/Nelson/Walsh*, 2000, 1.

301 *Landes/Posner*, 2003, 313; *Burk/Lemley*, 89 Va. L. Rev. 1575, 1628 (2003).

302 Such as circuit designs, materials, packaging, manufacturing process, and the like.

303 *Burk/Lemley*, 89 Va. L. Rev. 1575, 1628 (2003).

304 *Bessen/Maskin*, 1999, 2-3 ("complementary" was meant that each potential innovator takes a different research line and thereby enhances the overall probability that a particular goal is reached within a given time.); *Bessen/Maskin*, 1999, 11-13 (also noting that distinctive pattern of cross-licensing in these industries).

305 *von Hippel*, 1988, 53.

Companies not only have different reasons to patent across technologies,[306] but also different controlling power over the products.[307] An individual patent that can protect a whole product or a process is rare.[308] For example, in "complex technology", such as technologies involved in electronic products comprised of a large number of patentable elements, where a new commercializable product or process is comprised of numerous patentable elements,[309] firms rarely have proprietary control over all of the essential components of the products that they are developing.[310] It is difficult to have sole controlling power over products where standard-essential patents have to be exploited. Consequently, in these industries, patents are used as trading currencies.[311] By contrast, in "discrete technology" fields, such as drugs or chemicals, which are comprised of relatively few patentable elements,[312] firms often have full power to control their products and, as a result, patent exclusivity provides significant benefits.[313]

b) Patent protection in the pharmaceutical industry

The pharmaceutical industry has been famously dependent upon patent protection to recover its R&D costs.[314] The profit power of innovative drugs overwhelmingly hinges upon the extent to which the patent rights cover the

306 *Cohen/Nelson/Walsh*, 2000, 30.
307 *Cohen/Nelson/Walsh*, 2000, 19; *Kash/Kingston*, 28 Sci. & Pub. Pol'y 11 (2001).
308 *Scherer/Ross*, 1990, 624.
309 *Kash/Kingston*, 28 Sci. & Pub. Pol'y 11 (2001); *Cohen/Nelson/Walsh*, 2000, 19.
310 *Cohen/Nelson/Walsh*, 2000, 19.
311 *Kash/Kingston*, 28 Sci. & Pub. Pol'y 11, 16 (2001.).
312 *Cohen/Nelson/Walsh*, 2000, 19; *Merges/Nelson*, 90 Colum. L. Rev. 839, 911 (1990) (noting invention in chemical industry has discrete and cumulative features).
313 *von Hippel*, 1988, 53.
314 *Eisenberg*, 5 Yale J. Health Pol'y L. & Ethics 717, 721 (2005); *See also Weissman*, 25 U. Pa. J. Int'l Econ. L. 1079, 1085-94 (2004) (noting that pharmaceutical industry keep insisting stronger patent protection); *Kash/Kingston*, 28 Sci. & Pub. Pol'y 11, 21 (2001) (asserting the need of change the emphasis of patent system on serving large firms in simple technologies); *Mansfield/Schwartz/Wagner*, 91 Econ. J. 907, 913-915 (1981); *Jaffe/Lerner*, 2004, 39-41; *Cadot/Lippman*, 1995, 3; *Levin et al.*, 1987 Brookings Paper on Econ. Activity, 783, 824 (1987) (noting pharmaceutical industry is one of the few in which patents really do seem to matter); *Harhoff*, 2009, 32 (noting "impact of patent protection is particularly pronounced in the field of pharmaceuticals"); *Abramowicz/Duffy*, 120 Yale L.J. 1590, 1615 (2011); *contra*, *Boldrin/Levine*, 2010, 212 *et seqq*.

product.[315] The existence of this relationship can be seen in the fact that the pharmaceutical industry and the chemical industry are not influenced by increases in the cost of patenting.[316] The expectation of patent protection plays a more important role.[317] It has been empirically shown that when more patent protection is provided, greater R&D productivity occurs in pharmaceuticals and biotechnology.[318] Even a leading patent-sceptic economist, Nelson, mentions the need for patents to protect the product.[319]

The importance of the patent system matches well with the specificities of the pharmaceutical industry. To begin with, although pharmaceutical companies have very high fixed R&D costs, their marginal costs are very low, which means that they cannot help counting upon their patent and patent-protected revenues to recover their R&D expenditure.[320] As Landes and Posner properly point out, the greater the fixed costs of research and development, the greater the degree of patent protection required to create adequate incentives to invest in developing the invention in the first place.[321] Secondly, enormous uncertainties lining the path to the approval of a new drug and the resulting high failure rate seem to justify the importance of patents in this industry. [322] This means that patent protection allows pharmaceutical firms to capture much of the value of successful trials, even

315 *Kash/Kingston*, 28 Sci. & Pub. Pol'y 11, 14 (2001); *Cohen/Nelson/Walsh*, 2000, 23; *Bessen/Meurer,* 2008, 88-89 (noting pharmaceutical industry is atypically dependent on the patents, which is different from most other industries); *Glasgow*, 41 IDEA 227, 231 (2001).

316 *Lanjouw/Schankerman*, 114 Econ. J. 441, 454-55 (2004); *cf. Cohen/Nelson/Walsh*, 2000 (noting one of the reasons that people less use patent system is the costs of obtaining and enforcing patents).

317 *Scherer*, 2007, 1.

318 *Arora/Ceccagnoli/Cohen*, 26 Int. J. Ind. Organ. 1153, 1170-73 (2008) (further noting that it leads much less additional innovations in other industries such as electronics and semiconductors.).

319 *Mazzoleni/Nelson*, 27 Res. Policy, 273, 276 (1998) (noting "[t]he collection of small and medium sized firms in the American biotechnology industry is, of course, a striking example of enterprises that would not have come into existence without the prospect of a patent, and which depend on patent protection to make their profits, and to attract capital […].").

320 *Landes/Posner*, 2003, 313.

321 *Landes/Posner*, 2003, 295, 300; *Roin*, 87 Tex. L. Rev. 503, 537 (2009). It is in the same vein that the conventional rationale for granting patent exclusivity is the difficulty that a manufacturer may encounter while trying to recoup the investment in his R&D when the invention is readily copiable without protection.

322 *Scherer*, 2007, 33.

though it does not recover the cost of failed trials.[323] Thirdly, the fact that a pharmaceutical compound may be information rich can be one of the reasons why patent protection is provided in the form of a license for exclusivity on information.[324] Kitch notes that "the patent owner has an incentive to make investments to maximize the value of the patent without fear that the fruits of the investment will produce unpatentable information appropriable by competitors."[325] Even though the majority of information, the generation of which consumes time and money and from which generic producers are exempted, is usually produced after the patent filing and cannot be protected with patents,[326] nonetheless, patent exclusivity functions for innovators to recoup investment in the production of information. Fourthly, the ratio of the cost of innovation to the cost of copying makes patent protection a prerequisite to encouraging firms to invest in their R&D programs.[327] As Arrow argued, there would be little or no incentive for innovators to carry out innovation if the imitation cost is substantially lower than the cost of innovation.[328] Fifthly, the necessity of patent protection is clearly adducible from the fact that partners in the industry of the inventors in universities or government institutions are not willing to fund the development of drugs unless they are patent protected.[329]

B. Challenges and overcoming efforts

> "Conventional wisdom has long held that drug companies are a safe haven for capital during times of economic turbulence. People don't stop getting sick, the argument goes, so companies who make medicines should be insulated from all but the worst economic weather."[330]

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323 *Eisenberg*, 5 Yale J. Health Pol'y L. & Ethics 717,721 (2005).
324 *Nordhaus*, 1969, 70.
325 *Kitch*, 20 J. Law Econ. 265, 276 (1977).
326 *Eisenberg*, 5 Yale J. Health Pol'y L. & Ethics 717, 721 (2005); *Roin*, 87 Tex. L. Rev. 503, 511 (2009).
327 *See e.g., Mansfield*, 32 Manage. Sci. 173, 174-75 (1986) (reporting the survey results showing that 65% of new pharmaceutical would not have been introduced without patent protection).
328 *Arrow*, 1962.
329 *Owen-Smith/Powell*, 26 J. Technol. Transfer 99, 108 (2001); *Mazzoleni/Nelson*, 27 Res. Policy, 273, 276 (1998) (noting the patent protection has contributed for the small and medium sized firms to have survived and thrived).
330 *Holmes*, 379 Lancet 1863, 1863 (2012).

In addition to the above-cited conventional wisdom, pharmaceutical companies that are investor-owned and publicly traded entities, perform their duties very well, which are to provide shareholders with an optimal return on their investments.[331] Is the pharmaceutical industry still profitable, or is conventional wisdom these days being put to the test? Since 2000, the pharmaceutical industry has collectively destroyed shareholder value and showed a decline in R&D productivity.[332] Some investors have expressed doubts about receiving returns from drug developments, drug companies have been forced to reduce their R&D investments, and it has been reported that big pharmaceutical companies are struggling to gain returns on investments.[333] According to one report on R&D spending, the net present value and the number of new drug approvals showed that with the single exception of Novartis, the situation was not promising.[334] There have been several reports on cost-reduction plans by many companies that include reducing the number of employees and closing plants or research centers.[335] This aggressive reduction in jobs has been blamed in part on frugal insurers, generic competition, and a dearth of new medicines. [336] The estimates for top-line

331 *Avorn*, 309 Science 669, 669 (2005).

332 *Lindgardt/Reeves/Wallenstein*, 26 In Vivo: Bus. Med. Rep. 1, 1 (2008); *O'Hagan/Farkas,* Bain Insights [online] 1 (2009); *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 203 (2010).

333 *Jack*, Fin. Times, page 20, October 17, 2011.

334 *Jack*, Fin. Times, page 20, October 17, 2011 (reporting Company, R&D spending, Net present value of new drug approvals, and number of new drug approvals, respectively as follows: Roche, $35.1bn, $6.0bn, 2; Sanofi, $28.7bn, $10.2bn, 5; Novartis, $28.7bn, $37.7bn, 15; GSK, $28.3bn, 19.6bn, 16; AstraZeneca, $22.5bn, $7.1bn, 3; and Bayer, $10.6bn, $6.6bn, 3).

335 The world's largest pharmaceutical company, Pfizer, is continuing a cost-reduction plan including firing 19,000 employees, closing 8 plants and shutting 6 research centers. And even before this plan was enacted, Pfizer eliminated about 40,000 jobs during the 6 years till 2009, *see Randall*, Bloomberg, February 1, 2011; Soon after its anti-cholesterolemic pill Lipitor began facing generic versions, Pfizer has pledged to trim $1 billion from operations in 2012, *see Armstrong*, Bloomberg, April 12, 2012; U.K. drug maker AstraZeneca also announced to eliminate another 7,300 jobs, resulting its total job cuts over the last five years to almost 30,000, *see Whalen/Stovall*, the Wall Street Journal, February 2, 2012; In addition, AstraZeneca further announced it would cut 8,000 jobs worldwide in 2010; and GSK announced that 12,000 positions will be eliminated by 2014. *See Ellery/Hansen*, 2012, 26.

336 *Whalen/Stovall*, the Wall Street Journal, February 2, 2012.

growth for the leading pharmaceutical companies from 2013-2014 is not promising either.[337]

1. Decreased R&D productivity

There has been increasing concern about whether the pharmaceutical industry is facing an R&D productivity crisis. R&D productivity is the relationship between the value created by a new medicine and the investments required to generate that medicine.[338] In reality, however, it is not easy to measure either the value or the size of an investment. Thus, proxies are used to measure it.

R&D productivity can be gauged by outputs, such as patents, but this can be problematic, because the definition of patents has changed and certain industries can obtain patents more easily than others.[339] In 2012, Thomson Reuters provided a list of the top 100 global innovators based on their patenting activities.[340] The report was not based on all kinds of patents, but mainly on the companies' activities on "innovative" patents, which, according to its definition, means "the first publication in a patent document of a new technology, drug, business process, etc., [which] could also be called 'basic' patents."[341] As in 2011,[342] the pharmaceutical industry was ranked last.[343] While distinguishing the pharmaceutical industry as "molecule-focused" as compared to other industries that are "technology-focused", the report added that the pharmaceutical industry is nevertheless innovative.[344]

Ultimately, the targeted output of R&D of pharmaceutical companies are the available medications. Cockburn insists that the number of NMEs may

337 *Ellery/Hansen*, 2012, 26 (Top 10 pharma sales growth forecast: Pfizer, -1.7% growth; Novartis, 2.9% growth; GSK, 6.2%; Merck & Co., -0.6%; Roche, 1.9%; Sanofi, 2.5%; AstraZeneca, 1.4%; Johnson & Johnson, -0.5%; Abbott, -3.1%; Eli Lilly, -9.4%).
338 *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 204 (2010).
339 *Hunt*, 1999, 39.
340 *Thomson Reuters*, 2012.
341 *Thomson Reuters*, 2012, 4.
342 *Thomson Reuters*, 2011, 13.
343 *Thomson Reuters*, 2012, 12. Other industries ranked at the last were Agriculture & Forestry, Healthcare, Media/Internet, Petroleum, and Primary Metals.
344 *Thomson Reuters*, 2012, 18.

not be the proper proxy for the R&D program's true output for comparing low R&D productivity with high R&D expenditure.[345] However, he did not counterargue that the number of NMEs is a major measurement of productivity; he simply argued that a more accurate measure of R&D productivity in the pharmaceutical industry must include more factors than the number of NMEs.[346] Other factors that he insists be considered[347] prove only that the industry was working more on second generation inventions and products than on basic breakthrough inventions. He also notes that the declining counts of new drug approvals are "worrisome."[348] Furthermore, many analysts have carefully distinguished between the approval of NMEs and that of minor chemical modifications of existing drugs. The number of NMEs is one of the most representative indicators of pharmaceutical R&D activity, and NME development, as a whole, is therapeutically and economically significant.[349] Lastly, although patents and/or new chemical entities are not the best measures of R&D activity, much evidence on productivity is concentrated on these two measures.[350]

345 *Cockburn*, 2006, 4-11.

346 *Cockburn*, 2006, 4-11 (pointing out, from the input side, the value adjustment of inflation; from the output side, the much larger volume of approvals of minor chemical modifications, ii) significant variance of drugs value, iii) complete ignorance of incremental innovation and iv) time lag between the investment period and the time of market approval).

347 *Cockburn*, 2006, 5-10 (such as i) consideration of the much larger volume of approvals of minor chemical modifications of existing drugs, new formulations, dosage strengths, new combinations of already approved drugs, or new indication other than NMEs ii) significant variance of drugs in their scientific significance, health impact, and economic value while comparing breakthrough innovation and the "me-too" products; iii) complete ignorance of incremental innovation because of only focus on NMEs; and the like).

348 *Cockburn*, 2006, 25.

349 *DiMasi/Hansen/Grabowski*, 10 J. Health. Econ. 107, 108 (1991); *See also Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 204 (2010); *Higgins/Graham*, 326 Science 370, 370 (2009) (noting "[i]mprovements in pharmaceutical research and development (R&D) depend on product innovation. But the number of new compounds approved annually by the U.S. Food and Drug Administration(FDA) has fallen from an average of 35 in 1996-2001 to 20 in 2002-2007.").

350 *Grabowski/Kyle*, 2008, 273.

2. Dearth of new medical entities

a) Significance of NMEs

> "Statistical studies show an historical correlation since the 1950s between the number of new drugs introduced and declines in mortality and other health indicators across a wide range of diseases and health problems."[351]

NMEs are medications containing an active ingredient that has not been previously approved for marketing in any form.[352] The role of NMEs is vital to the morbidity and mortality of human beings. Further, newer drugs are significantly better than their predecessors in terms of greater efficacy, fewer side effects, and easier dosing.[353] Although the "drug-offset effect" - whether the use of a new drug reduces total health system costs - is arguable,[354] the development of new medication certainly provides net benefits to society.[355]

b) Decreased number of NMEs

Pharmaceutical companies invest vastly in R&D in the hope that this investment will produce new medications. However, it does not always turned out that way. The number of approvals of NMEs by the FDA provides a telling example. Although it concerns the number of approvals in only one country, since in the pharmaceutical industry globally the United States is its largest market, the figures are indicative of overall trends.[356] Although investment in pharmaceutical R&D has increased tremendously,[357] the num-

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351 *Cockburn*, 2006, 2-3, *Lichtenberg*, 5 Int. J. Health Care Fi. 47, 70 (2005) (reporting that launches of New Chemical Entities (NCEs) had a strong positive impact on the probability of survival, based on the relationship between the launches of new drugs and the longevity based on the data from 52 countries).

352 *See* subsection II.D.1.

353 *Cockburn*, 2006, 7.

354 *Lichtenberg*, 20 Health Affair. 241, 250 (2001) (arguing huge "drug-offset effect" meaning the use of certain new and effective drugs may reduce total health system costs; the savings can more than offset the increase in drug costs; therefore there might be net cost savings to society); *cf. Zhang/Soumerai*, 26 Health Affair. 880 (2007) (insisting the said drug-offset effect was not proven).

355 *Zhang/Soumerai*, 26 Health Affair. 880, 884 (2007).

356 *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 204 (2010).

357 See subsection III.A.1.b).

ber of new drugs approved by the FDA has remained consistently low over the last sixty years.[358] In particular, over the last decade, the cost of R&D has increased by around 70% with a reduction for the first time in 2009, while the output of NMEs on the market has seen a reduction of around 40%, despite a slight increase in 2009.[359] (See Figure 4) Even if one treats NME output as stable, taking the increased R&D expenditure and the scientific progress of technology into account[360] reveals the number of potential NMEs has incontestably fallen. Additional statistics show that only some newly marketed medications are breakthrough drugs,[361] the first in their class,[362]

358 *Munos*, 8 Nat. Rev. Drug Discov. 959, 959 (2009) (further noting until 1980, the trend line is basically flat; for the next 15 years, the slope gently upwards; and since 1996, approvals have dropped to their historical range.); *See also Pisano*, 2006, 118 (noting this phenomenon suggests "we are spending more but getting less."); see as another example, *Carmichael*, News Wk. May 15, 2010 (noting from 1996 to 1999, the U.S. FDA approved 157 new drugs, while during the comparable period, from 2006 to 2009, only 74 drugs were approved). There was a peak in 1996, which was speculated to be caused by the FDA processing a backlog of application on drugs awaiting approval; *Scherer*, 2007, 4-5.

359 *See also, Ellery/Hansen*, 2012, 4-5 (noting "the FDA approved half as many NMEs as in the period of 1996 - 2010").

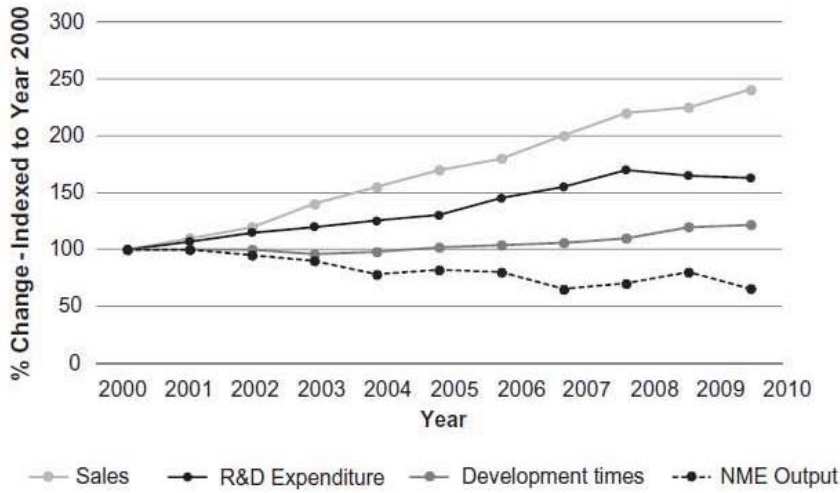
360 *Cockburn*, 2006, 17; For example, estimated number of "druggable targets" in the human body has risen from around 500 (*Drews*, 1999, 77) to over 3,000 after the human genome project. *See Hopkins/Groom*, Nature Rev. Drug Discov. 727, 728 (2002); *Russ/Lampel*, 10 Drug Discov Today. 1607, 1607 (2005) (suggesting the count is up to 3,000).

361 *Morgan, et al.*, 331 Brit. Med. J. 815, 815 (2005) (reporting in Canada between 1990 and 2003, only 6% of new drugs met the "breakthrough drugs" criteria, and 88% of new drugs did not provide a "substantial improvement" over existing drug products.); *Patented Medicine Prices Review Board*, 2005, 11 (defining the breakthrough drugs as "the first drug to treat effectively a particular illness or which provides a substantial improvement over existing drug products" while distinguishing from other medicines).

362 *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 203 (2010) (reporting out of 21 and 24 new drugs approved by the FDA in 2008 and 2009, only 29% and 17% could have been considered first-in-class.); cf. *FDA*, 2011, 4, 13-17 (reporting approval of 35 NMEs in 2011 including two new treatments for hepatitis C (boceprevir and teleprevir), the first new drug to treat Hodgkin's lymphoma in 30 years (brentuximab vedotin), and the first new drug to treat lupus in 50 years(belimumab)).

or treated disorders in a novel way.[363] These statistics indicate that the number of truly innovative new medicines approved by the regulatory bodies around the globe is decreasing.[364]

Figure 4: Global R&D expenditure, development times, global pharmaceutical sales and new molecular entity output in 2000-2010.[365]



In particular, chronic disorders such as diabetes, obesity, Alzheimer's disease, Parkinson's disorder, and schizophrenia still do not have efficient and tolerable medications, and no new broad-spectrum antibiotics have been marketed in almost 40 years.[366]

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363 *NIHCM*, 2002, 3 (Only around 35% of FDA newly approved drugs between 1989 and 2000 were based on new molecular entities that treats diseases in novel ways and most of approvals contained marketed active ingredients, and remaining 65% contained marketed active ingredients. Of these 65%, 54% of approval (incrementally modified drugs: IMDs) were only differed from the marketed product in dosage form, route of administration, or were combined with another active ingredient, and 11% of approvals were identical to products already available on the U.S. market.).

364 *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 203 (2010).

365 *Arrowsmith/Harrison*, 2012, 11 (originally reproduced from *CMR International 2011 Pharmaceutical FactBook* and the widening gap between the global sales and R&D curves may be attributable to the rise in generic drug sales).

366 *Cockburn*, 2006, 3.

c) Potential reasons for the decrease

In addition to the uncertainties discussed in above chapter A.1.c), the following reasons may explain the decrease.

(1) Decrease in solvable scientific problems

Since there are still many diseases that are not well understood, researchers must depend to a large extent on serendipity.[367] Despite the sky-rocketing incidence and severity of antimicrobial resistances, which seriously impact the management of infections such as malaria, tuberculosis, pneumonia, and AIDS, pipelines for anti-infective agents have also been dry, and pharmaceutical companies have been halting their research in this area.[368] The less costly scientific problems were resolved in previous decades, leaving the industry with only the complex and systemic problems, such as Alzheimer's.[369] The shift in focus to more complex disorders, such as Alzheimer's, strokes, obesity, diabetes, and arteriosclerosis, where there is a high degree of unmet medical need, has confronted the industry with huge challenges.[370] The challenge to find efficient treatment paradigms is enormous, since the biochemistry and the disease pathology underlying complex disorders are much more difficult and expensive to investigate, which has naturally resulted in the design of highly sophisticated clinical study protocols to show both efficacy and safety in humans.[371]

367 *Dutfield*, 2009, 296.
368 *Talbot, et al*., 42 Clin. Infect. Dis. 657, 665-666 (2006) (reporting some causes, such as relatively small size of market and unpredictability); *Norrby/Nord/Finch*, 5 Lancet Infect. Dis. 115, 116-117 (2005) (pointing out more rapid emergence of resistance of antimicrobials having higher sales figures as one of the reasons why the companies are leaving this field).
369 *Cockburn*, 2006, 14.
370 *Federsel*, 18 Bioorgan. Med. Chemistry 5775, 5777 (2010); *Cockburn*, 2006, 14-15.
371 *Federsel*, 18 Bioorgan. Med. Chemistry 5775, 5777 (2010); *Cockburn*, 2006, 14.

(2) Stringent safety regulations

More stringent safety regulations are among the best explanations for the decrease.[372] While tough regulations are indisputably appropriate, they make it more likely that several drugs which could have provided substantial benefits for patients despite their side effects have been weeded out. In fact, if current safety standards had been applied, even Aspirin® and Tylenol® might well have not been approved.[373] However, this is not to imply that relaxing safety regulations would be a desirable solution.

(3) Problem of over-disclosure

In the field of pharmaceuticals, there is a tendency to early and over disclosure, owing not only to the way in which research is published and the norms of academic publication, but particularly with respect to patenting practice in the industry. Firstly, researchers in universities rush to disclose their results by publishing them in well-known scientific journals, which reward them more, before trying to secure patent rights over them.[374] Secondly, on the one hand, it is relatively easy to show the structure of something being invented in the field of chemistry without actually having done it. A skilled person in the art can easily draw a chemical structure and make quite an accurate assumption about its physicochemical properties.[375] On the other hand, this disclosure can be more than sufficient to destroy the novelty of a compound which may show a promising effect and can be developed further. Thirdly, while a Markush type claim is an extremely helpful tool when claiming a large number of compounds,[376] using them can theoretically disclose and ruin the futures of millions of potential medications.

Last but not least, pharmaceutical companies file patent applications at very early stages in the R&D process, sometimes when they are still selecting a lead compound from numerous candidates. Thus, the patent applications may disclose a group of compounds as broadly as possible, while the appli-

372 See subsection III.A.1.a); *Dutfield*, 2009, 295-96; *Federsel*, 18 Bioorgan. Med. Chem. 5775, 5777 (2010).
373 *Dutfield*, 2009, 295-96.
374 *Roin*, 87 Tex. L. Rev. 503, 527 (2009).
375 *See e.g., Szabo,* IIC 1995, 457, 484-85.
376 See *supra* 104 -109 and accompanying texts.

cants have not decided yet which one they will develop. When its relevant properties are either disclosed prematurely or reasonably predictable at the time of invention, it is unpatentable regardless of whether its efficacy has already been proven, which might mean society would not have access to the potential medications.[377] Consequently, since such potential medications would no longer represent opportunities for investment, not only the medications themselves but also the second generation products therefrom would be unlikely to appear on the market.

(4) Early and numerous abandonments of potential candidates

The over-disclosure problem becomes more serious in conjunction with scrutinized go/no-go decisions.[378] This decision making process is a regular practice, and from the outset of R&D activities, pharmaceutical companies start to screen the patentability of their drugs.[379] As a result, the ones with weak or no patent protection or the ones which may infringe others' patents will be eliminated from the candidate list and will seldom be developed for medical use.[380] Companies eliminate the candidates as early as possible, because the cost of terminating the project at an early stage is obviously less.[381]

The real problem here is that an NME that may succeed in reaching the market is one of the thousands of compounds in the patent claim, and the rest may not be developed further. For the patent holder, the clock on their patent terms has started to run long before, and they expect that the window of potential market exclusivity is too diminished to recover their investments. Other potential investors have little incentive to invest in them either because of concerns about patent infringement or because they doubt their potential to recoup the investment even without patent exclusivities.

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377 *Roin*, 87 Tex. L. Rev. 503, 517-545 (2009).

378 See *supra* 249 and accompanying texts; *Roin*, 87 Tex. L. Rev. 503, 569 (2009).

379 *deStevens*, 1990, 266 ("Needless to say, the lead structure series must be patentable."). After this initial screening of patentability, the candidates would go through at least twice more screening before clinical trials, such as before the filing of patent applications and before the first clinical trials. The last audit is regarded as a "gate-keeping event" before the commencement of clinical trials.

380 *Roin*, 87 Tex. L. Rev. 503, 507 (2009).

381 *Pisano*, 2006, 145; *Dickson/Gagnon*, 3 Nat. Rev. Drug Discov. 417, 419-420 (2004) (noting the late stage failures are extremely costly).

3. Patent cliffs of blockbuster medications

One distinguishing feature of the field in the mid 1980s and 90s was the generation of high revenues from the sale of blockbuster drugs which were protected by patents. However, these blockbuster drugs came up against the so-called patent cliff, which refers to the sharp fall in profits caused by competition from generic versions of medications after expiration of the patents on those drugs, and is one of the most widely publicized challenges that big drug companies face.[382] In the U.S., this phenomenon was triggered by the introduction of a key legislative change, the Drug Price Competition and Patent Term Restoration Act 1984 ("Hatch-Waxman Act") with the Bolar exception, which allowed generic manufacturers to enter the market merely by proving bioequivalency.[383] Generic competition has increased in several respects, which are typically observed after the blockbuster drugs' patents expire.[384] For example, sales in the United States of the world's best-selling drug, Lipitor®, dropped by around 40% in the last three months of 2011 compared with the same period a year earlier, despite measures taken to maintain its sales.[385] The fate of Pfizer's Lipitor® ($5.3 billion in the 2010 in U.S. American market) was followed by Eli Lilly's antipsychotic drug Zyprexa® ($2.5 billion), Johnson & Johnson's antibiotic Levaquinin® ($1.3 billion), among others.[386]

4. Frequent merger and acquisitions (M&As) and in-licensing

The pharmaceutical industry has been characterized by both significant consolidation of large pharmaceutical firms and the vertical disintegration of the R&D process. A study has shown that eight of the top ten ranked phar-

382 *Holmes*, 379 Lancet 1863, 1863 (2012); *Whalen/Stovall*, the Wall Street Journal, February 2, 2012.

383 *See* subsection V.C.1.b).

384 *Grabowski/Kyle*, 28 Manage. Decis. Econ. 491, 496, 501 (2007).

385 *Holmes*, 379 Lancet 1863, 1863 (2012).

386 *Alazraki*, Daily Finance February 27, 2011 (further reporting Bristol-Myers Squibb and Sanofi-Aventis' anti-platelet drug Plavix (6.1 billion$), AstraZeneca's antipsychotic drug Seroquel (3.7 billion$), Merck's anti-asthmatic drug Singulair (3.2 billion$), Takeda's anti-diabetes drug Actos (3.4 billion$), and Amgen's anti-arthritis drug Enbrel (3.3 billion$) would lose their patent protection in 2012.); *see also Wilson*, The New York Times, March 6, 2011.

maceutical companies in 2004 had completed major *mergers* with other pharmaceutical companies, with two notable exceptions, Merck and Johnson & Johnson.[387] Traditional economic motives for mergers, such as increasing market share and marketing power to gain competitive advantage, have not been major issues in large pharmaceutical mergers.[388] Various researchers have pointed out that companies in economic distress with pipeline gaps, ageing portfolios of marketed drugs, and expired patents for major products are more likely to engage in mergers and acquisitions.[389] Along with these factors,[390] higher R&D costs have been also cited as one of the main factors underlying the trend toward more mergers and industry consolidation.[391] Although some companies have contended that these mergers were intended to pursue R&D efficiencies, the benefits from increased size and diversity were reported as less than expected,[392] and there is still little evidence that the mergers have increased long-term R&D performance or outcomes.[393]

Along with M&As, there has been a significant shift toward *license-in* technology from biotechnological companies and small and medium enterprises ("SMEs") to reduce R&D costs and effort. [394] While facing and preparing for the eventual patent expiry of their own best sellers and the resulting revenue loss, innovative companies, such as Pfizer, which saw its Lipitor patent expired in 2011, and Bristol-Myers, which saw its Plavix patent expired in 2012, have focused on acquiring small biotech compa-

387 *Grabowski/Kyle*, 2008, 263-64 (other eight companies: Pfizer, GlaxoSmithKline, Sanofi-Aventis, Novartis, AstraZeneca, Roche, BMS, and Wyeth).

388 *Grabowski/Kyle*, 2008, 270.

389 *Higgins/Rodriguez*, 80 J. Financ. Econ. 351 (2006); *Danzon/Epstein/Nicholson*, 28 Manage. Decis. Econ. 307, 307 (2007); *Burgess/Terblanche*, 3 Open Access J. Clin. Trials 45, 45 (2011) (noting M&As are attempts to retain profitability). One report estimated sales at risk from patent expiration would be over 183 billion USD in 2011/14 (*EvaluatePharma*, 2009, 6); *Munos*, 8 Nat. Rev. Drug Discov. 959, 965-66 (2009) (noting revenue losses caused by the expiration of patents on key blockbuster drugs with continuing the current business model may result in a reduction of 5~10% in sales and 20~30% in new income in 2012-2015.).

390 *Grabowski/Kyle*, 2008, 262.

391 *DiMasi/Hansen/Grabowski,* 22 J. Health Econ. 151, 152 (2003).

392 *Henderson*/*Cockburn*, 27 RAND J. Econ. 32, 53 (1996).

393 *Grabowski/Kyle*, 2008, 283; *Munos*, 8 Nat. Rev. Drug Discov. 959, 965 (2009) (noting "[f]or now, the evidence suggests that M&A can help small companies, but are not an effective means to boost NME output among larger companies.").

394 *Holmes*, 379 Lancet 1863, 1863-64 (2012).

nies.[395] These kinds of alliances or in-licensing can also function as previous measures before the mergers and acquisitions in the pharmaceutical area.[396] Many research-based pharmaceutical companies are also quite active in the *generic business* directly, through affiliate companies, or mergers with generic companies.[397] These activities, such as M&As, in-licensing, or engagement of generic business can be understood as ways of investing money in other businesses which are less risky and less costly.

5. Drastic increase of second generation inventions

> "Because it gets more and more difficult and expensive to find and develop new drugs, more effort is being put into finding ways of delivering existing drugs more effectively."[398]

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395 *Thomas*, The New York Times, May 1, 2012.

396 *Higgins/Rodriguez*, 80 J. Financ. Econ. 351, 352-53 (2006).

397 For example, a Japanese pharmaceutical company, Daiichi-Sankyo took 35% stake in an Indian generic drug maker, Ranbaxy. *See Anonymous*, New York Times, June 11, 2008; Pfizer announced it had entered into major licensing agreement with three India-based pharmaceutical companies, such as Aurobindo Pharma Ltd., Claris Lifesciences Ltd. and Strides Arcolab, thereby adding new non-Pfizer products to its portfolio, see *Pfizer*, Annual Review 2009, 27; Also while announcing "[g]enerics are an increasingly important part of Sanofi-aventis' plans to become a diversified global healthcare company", Sanofi-Aventis announces it has created the third largest generic company in the European market by unifying the Group's generic activities under the name of Zentiva. *See Zentiva*, Zentiva Press Release, Apr. 4, 2011; Most representatively, Novartis grouped together the generic sections under the name of Sandoz in 2003; subsequently acquired BASF Generics, Lec, Hexal, and Eon; an reached the second biggest generic company in the world after Israeli company, Teva. *See Ellery/Hansen*, 2012, 27; Also the generic companies buy innovative companies. For example Teva not only acquire the generic companies, such as US company - Barr pharmaceuticals or German one - Ratiopham; but also it completed its acquisition of US biopharmaceutical company, Cephalon in 2011. *See Teva*, Teva News Release, Oct. 14, 2011.).

398 *Grubb/Thomsen*, 2010, 258.

a) Life cycle management or evergreening

The incentive to maximize the monopoly period of brand name drugs is huge.[399] Different strategies are pursued by pharmaceutical firms to maximize the exclusivity of their particularly successful drugs,[400] which are collectively known as "evergreening" or "life cycle management."[401] Others refer to these strategies as "line extensions" or "product reformulation." Whatever the term used, through these methods pharmaceutical firms increase R&D costs on second generation inventions, heighten barriers to market entry that may become excessive, and thereby restrict competition beyond the 20-year patent term.[402] Some refer to this as building "patent walls" in the attempt to broaden the scope of the basic patent.[403] This phenomenon is well recognized as important by the industry[404] and markedly noticeable when the companies are heavily dependent on a small number of highly profitable products;[405] or when the product is a so-called "blockbuster", just as generic competition is directed at products achieving larger markets. Angell argues that the pharmaceutical industry has been "ingenious in finding ways to extend patents on its bestselling drugs."[406] Firms can move the high pricing potential of NMEs to second generation products by effectively modifying older products in order to make them attractive.[407] When

399 *Dutfield/Suthersanen*, 8 Intell. Prop. Q. 379, 389 (2004); *Glasgow*, 41 IDEA 227, 232 (2001).

400 *Dutfield/Suthersanen*, 8 Intell. Prop. Q. 379, 389 (2004); *Glasgow*, 41 IDEA 227, 233-254 (2001).

401 See e.g. *GSK*, 2011, 1 (noting "'[e]vergreening' is an inherently pejorative term.").

402 *Gaudry*, 29 Nature Biotech. 876, 876 (2011); *Dutfield/Suthersanen*, 8 Intell. Prop. Q. 379, 389 (2004); *Shadowen/Leffler/Lukens*, IIC 2011, 698, 699; *Rathod*, 7 J. Generic Medicines 227, 227 (2010) (defining "evergreening is a strategy by which technology producers, using serial secondary patents and other mechanisms, keep their product sales protected for longer periods of time than would *normally* be permissible under the law.").

403 *Hopenhayn/Mitchell*, 32 RAND J. Econ. 152, 163 (2001).

404 *Ellery/Hansen*, 2012, 3-4 (a series of interviews with pharmaceutical industry executives in a survey conducted on pharmaceutical lifecycle management in 2004 reported that the executives felt that LCM had been important, and 90% predicted that its importance would growing during 5 years following the report publication (2006-2010), while 60% expecting it to become much more important.).

405 *Dutfield/Suthersanen*, 8 Intell. Prop. Q. 379, 389 (2004).

406 *Angell*, 342 New Eng. J. Med. 1902 (2000); cf. *Holmer*, 343 New Eng. J. Med. 1415 (2000).

407 *NIHCM*, 2002, 4.

the line extension is positioned and designed properly, it can improve the value proposition and the whole status of the previous NME,[408] thereby driving revenue growth. In the 1990s, when the evergreening practice first appeared, second generation inventions were polymorphs, metabolites, enantiomers, change in strength/dosage and the like. Since then, however, the list of second generation patents has lengthened to include patents on a much larger number of characteristics, such as impurities/substantially pure compounds, new methods of use, additional process, new dosing route, packaging/patient instructions, pharmacokinetic/pharmacodynamic parameters regarding drug delivery system, combination with other drugs, segmented patient populations, and the like.[409]

In addition to the companies who hold patents for original active ingredients, other companies will seek to obtain patents on second generation inventions.[410] Indeed, an empirical study conducted in Australia has found that there are substantial patenting activities undertaken by companies other than originators of high-cost drugs, including generic companies.[411] Numerous forces have joined to encourage manufacturers to modify drugs that are already on the market. Firstly, pharmaceutical firms may expect it to be vastly less time-consuming, expensive and risky to invest in the R&D of second generation medicine containing an active ingredient whose safety and efficacy have already been established.[412] The development of one or even many line extensions can be much easier than that of an NME. Secondly, if the original manufacturers are the developers of next generation drugs, they can benefit from the experience already gained from the basic substance.[413] Furthermore, since they already have real market experience, the companies already know the potential concerns.[414] Thirdly, other frame-

408 *Ellery/Hansen*, 2012, 15, but it would be difficult to get a premium price over the original.

409 *See e.g.*, *Rathod*, 7 J. Generic Medicines 227, 229 (2010); *Dutfield/Suthersanen*, 8 Intell. Prop. Q. 379, 389 (2004), *Parthasarathy/Goddar*, IIC 2009, 38, 41 (noting secondary inventions including new versions of the active compound such as enantiomers, salts, esters, or polymorphs, or new uses of a drug, the metabolite of a prodrug, and the like).

410 *Dutfield/Suthersanen*, 8 Intell. Prop. Q. 379, 389-90 (2004) (the other firms will be willing to license their patents to the original patent holders.).

411 *Christie, et al*, 8 PLoS Med 1, 6 (2013).

412 *NIHCM*, 2002, 4.

413 *Landes/Posner*, 2003, 330.

414 *Ellery/Hansen*, 2012, 15.

works of protection, especially market exclusivity by regulatory regimes, rewards manufacturers for making even modest changes to their products by providing three years of market exclusivity for the new version of the product, the new use, new dosage form, new route of administration, or combinations of older drugs, and the like.[415] Fourthly, as some scholars have affirmed, this phenomenon has bolstered the at-risk revenues by the generics' challenges to their basic patent. [416] Lastly, there are other driving forces, such as remarkable advances in the drug delivery system and separation technology of a single component, regulatory promotion for the IMDs,[417] an effective mechanism to prevent generic entry by acquiring patents on IMDs (+ 30 months' automatic stay[418] in the United States) and the like.[419]

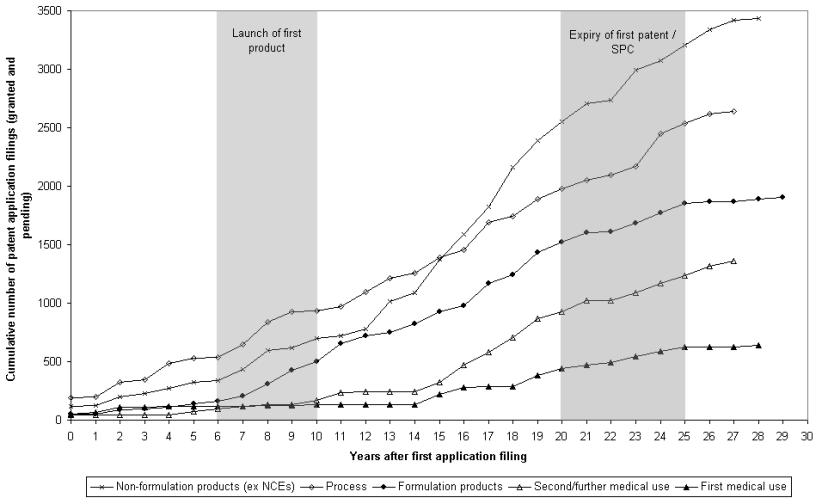
b) Drastic increase of this activity supported by the number of second generation patents

One study analyzing drugs that were associated with at least one patent and approved by the FDA from 2000 to 2010 reported that drug companies frequently explored the evergreening strategy.[420] It was further reported that the phenomenon of acquiring additional patents, whose validity or applicability are often dubious, have increased.[421] It was estimated that about 30% of R&D spending is devoted to bringing "line extensions" to market.[422] A report of the European Commission on the pharmaceutical sector[423] further identified the following trends: i) A markedly sharp increase in the number of patent applications in pharmaceutical inventions was observed during the period of 2000 to 2007;[424] ii) 93% of the pending applications were classified

415 *NIHCM*, 2002, 4, 15-18; Title 21 United States Code - Food and Drugs ("21 U.S.C.") § 355; Council Directive 2001/83/EC, Art. 10.
416 *Higgins/Graham*, 326 Science 370, 370 (2009).
417 e.g. 505(b) way of the 21 U.S.C.
418 *See infra* 1221 and accompanying texts.
419 *NIHCM*, 2002, 15-18.
420 *Gaudry*, 29 Nature Biotech. 876, 876 (2011).
421 *Engelberg/Kesselheim/Avorn*, 361 New Eng. J. Med. 1917 (2009); *Hemphill/Sampat*, 31 J. Health Econ. 327, 327 (2012).
422 Cited in *Frank*, 22 J. Health Econ. 325, 327 (2003).
423 See DG competition, 2009.
424 This statistics was based on the IPC (International Patent Classification) A61K with some exceptions (e.g.: preparations for dentistry(A61K6) and so on), which can be regarded as the closest proxy for pharmaceutical applications.

as selection inventions;[425] and iii) 84% of the granted patents were categorized as selection inventions. Clearly, the number of patents for selection inventions had soared.

Figure 5: Patent portfolio life cycles as a function of claim types for the top 20 INNs by total sales (2000 –2007).[426]



The uppermost line in Figure 5, which shows the cumulative number of patent applications for non-formulation products (such as salts, particles, polymorphic forms, and so on, except NCEs), provides evidence of the trend toward patent filings for selection inventions which are the focus of this paper. Even though it represents the cumulative number of patent filings, this line indicates a marked preference for second generation invention re-

425 The terminology in the pharmaceutical Sector Inquiry is "secondary patent (application) " which is an application not related to the first the patent (application) for the active molecules for which the contrary category of "primary patent (application)" is used.

426 *DG competition*, 2009, 179.

lated claims.[427] It is clear that life cycle management strategies have brought the industry to a more complex and confusing patent landscape for nearly all drug patents.[428]

C. Summary

The pharmaceutical industry is one in which the economic rationale for patents works to protect inventors from imitations and provides incentives to bear the cost of innovation.[429] The patent system is therefore highly effective, and its protection is essential.[430] However, even though the patent system as it has existed for some time, the number of real medicines has not changed, which challenges the theory that patent protection provides incentives for real medicines and promotes progressive technological development in this field. As has been argued in this chapter, this industry is facing challenges, such as a decline in performance so that fewer products are reaching the market, with concomitant losses of billions of dollars in revenue as some of the blockbuster medications go off patent, the cost of developing new drugs and conducting clinical studies spirals, more stringent regulatory requirements are imposed, and healthcare systems become increasingly cost-constrained.[431]

> "Perhaps the industry has finally reached bottom, and it recognises the enormous need to look for a new business model."[432]

Thus, it has become increasingly important to have strategies to protect and to take full advantage of existing patents, or to invest assets in less risky and costly areas. A possible consequence of this is that the pharmaceutical in-

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427 *DG competition*, 2009, 179, the report was arguing there is clear trend for companies to file patent applications as the expiry date of the primary patent approaches. However, patents are only granted to the novel inventions, and there are many competitors in the same field of research. Thus, even if the companies want to file them as late as possible, the later they file applications, the more risks they will face to get a patent. Thus, above argument is not persuasive.

428 *Howard*, 4 J. Generic Med 231, 236 (2007).

429 *Bessen/Maskin*, 40 RAND J. Econ. 611 (2009).

430 *Roin*, 87 Tex. L. Rev. 503, 513-15 (2009); *Bessen/Meurer,* 2008, 88-89.

431 *See e.g., Federsel*, 18 Bioorgan. Med. Chem. 5775, 5775 (2010); *Paul*, *et al.*, 9 Nat. Rev. Drug Discov. 203, 203 (2010).

432 *Holmes*, 379 Lancet 1863, 1863 (2012).

dustry is led in a direction that might be lucrative but not well aligned with public health requirements.[433]

On the one hand, the number of NMEs is decreasing because of the over-disclosure problem in relation to the novelty requirement, more stringent safety regulations,[434] and for various scientific reasons, including the existence of diseases which are poorly understood,[435] and the shift of focus to more complex disorders, such as Alzheimer's, strokes, obesity, diabetes, and arteriosclerosis, where there is a high degree of unmet medical need.[436] On the other hand, the number of second generation patents is drastically increasing. One may argue that at least there are more patents and/or product inventions, which one hopes have been practically improved. However, one must consider whether more patents mean more and better innovations.[437] Moreover, companies other than the basic patentee are also seeking to acquire more patents for the second generation inventions and are becoming more dependent on those patents for cost reduction and product improvements, because they lack the first mover's advantages or the learn-by-doing knowledge of the basic patentees.[438] In this regard, Avorn argues that patent law guarantees a patent to manufacturers who make trivial changes in existing active ingredients, even if the "new" drug has the same clinical effect.[439] This can also allow companies to extend the life of a blockbuster product by making a virtually identical drug and shifting use to the new drug.[440]

Therefore, the dearth of NMEs is sensitive to a wide range of factors, which have been discussed at length in this chapter, and the increased number of second generation patents is influenced by several factors. The next chapter will analyze the role that patent law and the patent system have played in the changing landscape of pharmaceutical innovation.

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433 *Avorn*, 309 Science 669, 669 (2005).
434 *See* subsection III.B.2.c)(1).
435 *Dutfield*, 2009, 296.
436 *Federsel*, 18 Bioorgan. Med. Chemistry 5775, 5777 (2010) (noting this led to the design of highly sophisticated clinical study protocols to show both efficacy in man and safety); *Cockburn*, 2006, 14-15.
437 *Landes/Posner*, 2003, 325.
438 *Landes/Posner*, 2003, 330.
439 *Avorn*, 309 Science 669, 669 (2005).
440 *Angell*, 2004, 76.