



The Benefits of Incremental Innovation

FOCUS ON THE PHARMACEUTICAL INDUSTRY

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Summary

Steven Globerman

Technological innovation is widely understood to be a major stimulus to real economic growth and to improvements in society's standard of living. Hence, it is unsurprising that policy makers in Canada and elsewhere have long been focused on promoting innovation through policies such as tax incentives and intellectual property legislation. While less attention has been paid to the nature of innovation, there has been recent criticism that private-sector organizations are excessively focused on incremental innovation at the expense of so-called breakthrough innovation. Incremental innovations encompass relatively modest improvements to existing products and production processes, whereas breakthrough innovations are characterized by their scientific and commercial novelty, along with higher associated financial risk. The premise underlying calls for firms to focus more on breakthrough innovations is that the social benefits of breakthrough innovations dwarf those realized from incremental innovations, and that the differences more than justify the greater associated costs and financial risks.

Scepticism about the benefits of incremental innovation has arguably been most pronounced in the context of the pharmaceutical industry. Regulators in a growing number of countries are exhibiting increasing reluctance to approve so-called "me-too" drugs for sale on the grounds that they offer no significant benefits to patients. In fact, incremental innovations undertaken by drug companies provide great value for both physicians and patients. Specifically, they provide physicians with the flexibility to treat the individual needs of diverse patients with precision while improving patient compliance by eliminating adverse drug reactions and side effects. Incremental innovation also promotes increased price competition among drug manufacturers, thereby generating cost savings in the health-care sector.

The benefits to society from incremental innovation are documented in other industries besides pharmaceuticals. Indeed, incremental innovation is typically a critical stage of technological change in which the commercial value of scientifically novel inventions is greatly enhanced, thereby expanding the

number of potential adopters of the new technology. A relevant example is the jet engine, which suffered from unacceptably low performance characteristics until materials were made available to withstand high temperatures and pressures. Furthermore, the knowledge and experience gained from incremental innovation often provides the basis for the future development of relatively novel innovations. This phenomenon is illustrated by Canon's "revolutionary" 35mm camera, which drew upon that company's core knowledge of precision optics and mechanics that, in turn, derived from Canon's experience making photocopiers.

The history of technological change in pharmaceuticals and other industries should serve as a caution against public policies that seek to discourage incremental innovation in favour of initiatives to create breakthrough innovations. While critics argue that incremental innovation represents a waste of resources and conveys only minor improvements upon existing products and production processes, the evidence indicates that they are misguided. This is arguably particularly true in the case of pharmaceuticals where there is abundant evidence documenting the benefits to society from incremental innovation.

Do Private Sector Companies Do Too Much Incremental Innovation?

Steven Globberman

1. Introduction

The marked slowdown in the real economic growth of developed western economies over the past few decades has raised important concerns about whether the main sources of economic growth have dried up and, therefore, whether the developed economies should no longer count on continuing increases in real per-capita income levels that have characterized those economies over most of the post-WWII period. A number of economists, most notably Robert Gordon of Northwestern University, have identified stagnating productivity growth as the major reason for projecting very low growth rates in per-capita real income for the United States and, presumably, Canada over the foreseeable future.¹ According to Gordon, the primary reason for this very unfavourable outlook is the dearth of “great inventions” such as those that were introduced in the century from 1870 to 1970. These include electricity, the internal combustion engine, running water, and indoor plumbing. Gordon’s view is that western societies have reached a scientific plateau such that there will be a decline in the usefulness of future inventions in comparison with the great inventions of the past.²

While Gordon is particularly pessimistic about the future of technological change, there is no shortage of scholars and policy makers who argue that companies, including those in the United States and Canada, are engaging

Chapter 1 in Steven Globberman and Kristina M. Lybecker, *The Benefits of Incremental Innovation: Focus on the Pharmaceutical Industry*. © 2014 Fraser Institute <<http://www.fraserinstitute.org>>. The author thanks Kristina M. Lybecker for many helpful suggestions to improve the essay. He also thanks Bacchus Barua and two reviewers for their insightful comments and criticisms.

1. See Gordon, 2013. By way of perspective, the standard of living in the United States and Canada has historically doubled every 35 years. Gordon projects a future doubling of the US standard of living to take at least 100 or more years.

2. It should be noted that Gordon’s pessimistic view about future rates of growth of per-capita income is predicated on factors besides slower rates of technical progress such as a slowing accumulation of human capital as measured by high school and college graduation rates.

in too much “imitative” innovation and too little “breakthrough” or “disruptive” innovation. The distinctions that have been drawn in the literature among different types of innovation will be discussed in a later section of this essay. The specific observation I shall make here is that it is impossible, as a practical matter, to draw any bright-line distinctions between different types of innovation. Nevertheless, the basic criticism that private-sector organizations allocate their resources inefficiently when it comes to innovation activity deserves to be addressed on both theoretical and empirical grounds against the background of the aforementioned evidence of a pronounced slowdown of productivity growth in developed economies.

This essay contains a general assessment of the argument that private-sector companies spend too much money on imitative innovations relative to what they spend on breakthrough innovations from the perspective of society’s welfare, and that government policies are needed to correct what amounts to a market failure.³ While this argument has influenced public policy most significantly in the pharmaceutical industry, there are growing calls for companies generally to emphasize so-called disruptive innovations and to de-emphasize incremental technological advances (see, e.g., Seidman, 2013). Such calls are ostensibly based upon the idea that technological progress and its contributions to economic growth stem disproportionately from radical innovations, and that private-sector organizations, either through inertia or “excessive” risk aversion, eschew making radical changes to existing products and production processes in favour of modest changes.⁴ While the literature has traditionally focused on the issue of market failure in the creation of new products and production processes generally, the broad purpose of this essay is to assess the more specific argument that there is market failure in the type of innovation pursued by private-sector organizations.

The essay proceeds as follows. The next section sets out some distinctions among different types of innovation with a particular focus on situating incremental innovation along the spectrum of types of innovation. The key distinction in this regard is the degree of technological and/or commercial novelty of an innovation. Section 3 identifies and discusses theoretical arguments for anticipating that for-profit companies may do “too much” incremental innovation from the perspective of society’s economic welfare. Sections 4 and 5 present and assess empirical evidence drawn from the literature bearing on the relevance of the “market failure” arguments considered in Section 3. The final section provides a brief summary and conclusion. The main conclusion is that the evidence from historical innovation experience across a wide range of organizations and industries does not support the argument that for-profit firms do too much incremental innovation from a national economic perspective.

3. A more focused consideration of this basic issue in the context of the pharmaceutical industry is provided in the accompanying essay by Kristina M. Lybecker, pages 23–59.

4. Ironically, there is relatively little evidence on the financial value of R&D efforts to promote radical innovation. On this point, see Sorescu, Chandy and Prabhu, 2003.

2. Defining innovation

It is widely acknowledged that technological change is probably the most important source of improvements in the productivity of industries and, consequently, of gains in real economic growth and standards of living (see, e.g., Gold, Rosseger and Boylan, Jr., 1980). In turn, innovation is a critical stage in the process of overall technological change.

There are many definitions of innovation. In one way or another, all of the definitions equate innovation to changes in existing products or production and/or organizational processes that make those products and processes more commercially valuable. In the case of both innovative products and innovative processes, a fairly ubiquitous consequence of their introduction is that industrial and household adopters can carry out their industrial and domestic activities more efficiently than they could prior to an innovation's introduction. In some cases, they are able to carry out specific activities that they could not prior to the innovation, because the innovation relaxes technical or economic constraints. An illustrative example is the increasing speed of microchips and the growing number of transistors embedded in those chips. This development has enabled computers to carry out new and increasingly complex calculations and other tasks at ever-faster speeds. Another example is the wind-turbine engine. The Danish company Vestas incrementally improved the design of the generators powering the turbine so that the rotor blades could operate at varying speeds. This allowed the turbine to be used efficiently in locations experiencing different wind conditions.

Innovation, therefore, represents the early introduction of new products and production and organizational processes into the economy. It is distinct from the earlier invention stage of the technological change process that predates commercial introduction of new technology. It is also conceptually distinct from the later (diffusion) stage characterized by the widespread adoption of new products and processes, although modifications of products and processes inevitably occur as adoption takes place. Specifically, the adoption, or diffusion process, is typically characterized by improvements to the performance characteristics of the innovation, its modification and adaptation to suit the specialized requirements of specific sub-markets, and the introduction of complementary inputs that enhance the utility of the original innovation (Rosenberg, 1972).

As suggested in an earlier section, contributors to the literature on innovation have distinguished amongst different types of innovations in various ways; however, most of the relevant distinctions have to do with the degree of novelty of the innovation in question. For example, Baumol (2004) distinguishes between "revolutionary" and incremental innovative activities. The former encompass truly novel innovations. The latter encompass incremental improvements in user-friendliness, increased reliability, marginal additions to applications, expansions of capacity, and the like. Henderson (1993) identifies

a long-standing distinction in the literature between “radical” innovation and incremental innovation, where radical innovation is seen as making old technology obsolete, while incremental innovation is defined as routine predictable change that is a logical extension of existing knowledge. Henderson also distinguishes between radical and incremental innovation in the economic sense compared to the organizational sense. Radical organizational innovations require knowledge and operating procedures that are unfamiliar to firms, while incremental organizational innovations are complementary to incumbent firms’ operating procedures and accumulated knowledge.

Most distinctions among innovations follow along the lines suggested by Henderson. For example, Hill and Rothaermel (2003) also distinguish between incremental and radical innovations.⁵ They identify radical innovations as involving the development of a new technological paradigm that creates new knowledge and understanding and potentially new industrial sectors, whereas incremental innovation builds upon the existing knowledge base possessed by incumbent firms. In contrast, radical innovations involve methods and materials that are novel to the incumbents.

The consulting firm PwC identifies three types of innovation. The first, incremental innovation encompasses changes to existing products or services that are primarily aimed at protecting the innovating firm’s market share and maintaining profit margins. The second, breakthrough innovation, is characterized by more substantial changes to technologies and business models and, therefore, creates greater competitive advantages than incremental innovation. Radical innovation, the third type, creates drastic changes to the competitive environment for a product or service, or it creates even entirely new businesses. Such innovation can generate explosive growth in major new categories of products and services (PwC, 2013).

Sorescu, Chandy, and Prabhu (2003) also distinguish among three types of innovation. Specifically, they identify a radical innovation as a product that incorporates a new technology and that fulfills key customer needs better than existing products do. They identify a “market breakthrough” as providing substantially greater benefits than existing products, although the core technology is not significantly new. Finally, a technological breakthrough uses a substantially different technology than existing products without considerably increasing the benefits to consumers.

Baumol (2004) cautions that, while it is convenient to divide innovations into distinct categories such as “breakthrough” and “incremental”, in the real world many innovations fall into neither extreme category but are somewhere in between. Moreover, the discrete distinctions all seem to embody the characteristic of novelty (either technical or commercial) with associated

5. For a discussion of the practical difficulties in implementing the distinction between radical and incremental innovations, see Sorescu, Chandy and Prabhu, 2003.

risk and expected return attributes. Hence, for purposes of this analysis, it is arguably more useful to distinguish among innovations on the basis of their underlying technological and/or commercial risks. In this way, innovations can be characterized in a continuous fashion that is both more realistic and more amenable to the analysis described below. In this context, the degree to which an innovation is radical increases as its technical and/or its commercial success becomes less predictable. An innovation's technical success will ordinarily be less predictable, the more novel the underlying technological advances incorporated in the innovation. An innovation's commercial success should be more unpredictable, the smaller the pre-existing market for the innovation, other things constant. Conversely, innovations become "more incremental" as the novelty of the underlying technological change decreases and the pre-existing commercial market increases.

In summary, there is an extensive literature distinguishing among different types of innovation. The most important distinction is the technical and commercial novelty of the innovation. Since more novel innovations also tend to be more risky, so-called breakthrough or disruptive innovations can be characterized as more novel and risky than incremental innovations. The presumption is often made that breakthrough innovations provide greater private and social commercial benefits than do incremental innovations (See, e.g., Mewman, 2013). If this is true, individual firms must balance the expected larger private commercial benefits of successful breakthrough innovations against the increased risks associated with those innovations as compared to incremental innovations. A relevant public policy issue that arises in this regard is whether, for given investments in innovation, private-sector organizations will systematically under-invest in breakthrough innovations or over-invest in incremental innovations.

3. Potential for market failure in private-sector innovation

The distinctions drawn among different types of innovation basically acknowledge that potential commercial rewards are likely to increase as firms move along the spectrum from relatively modest changes to existing products and processes (incremental innovation) to relatively dramatic changes (breakthrough innovation). At the same time, this movement also obliges organizations to assume more risk (Cromer, Dibrell, and Craig, 2011). An efficient wealth-maximizing firm choosing an innovation strategy would presumably balance higher expected future profits against increased risk in order to maximize the welfare of its shareholders. Specifically, it would choose the degree of technical and commercial novelty of its portfolio of innovation projects so as to equate the benefit of increased shareholder wealth against the cost of increased risk to the shareholder. Put more simply, dedicating more resources to creating breakthrough innovations relative to incremental innovations imposes greater financial risks on the organization, at the same time as it should increase

expected profits. An efficient wealth-maximizing organization will choose the mix of breakthrough and incremental innovation that achieves a balance at the margin between shareholders' tolerance for risk and their expectations for profit.

In this regard, the risk-return trade-off facing the innovating organization is the same as that facing financial investors, and it is initially described in [figure 1.1](#). The vertical axis labeled *P* measures the expected return to shareholders from innovating, while the horizontal axis labeled *S* measures the expected risk to shareholders from innovating. As one moves up the vertical axis, the organization is expecting higher returns from its innovation portfolio. As one moves along the horizontal axis, the organization perceives increased risks associated with its portfolio of innovation projects. As noted earlier, there are essentially two broad types of risk. One risk is that the innovations undertaken will not meet technical requirements for successful introduction into the marketplace. The other is that the market's demand for the product will be smaller than the organization anticipated.

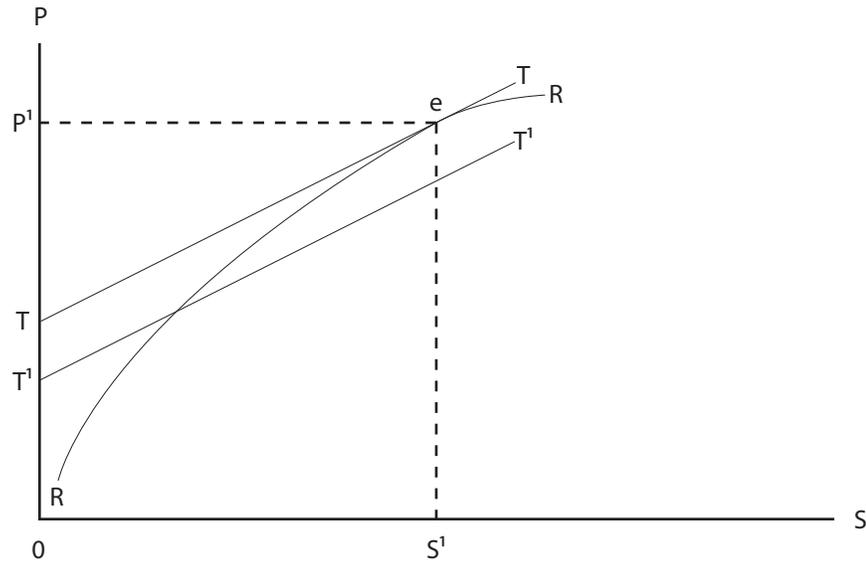
The curve labeled *RR* represents the expected returns that are attainable by the organization from various innovation projects along with the risks associated with undertaking those projects. The curve is upward sloping. This slope reflects the reasonable and widely accepted assumption that investments promising higher expected returns are ordinarily associated with greater risk to shareholders.⁶ The convex shape of the curve incorporates the idea that risk-adjusted returns to innovation decrease as more risky innovation projects are undertaken. Equivalently, the risk associated with increasingly novel innovations increases faster than the expected returns.⁷ The curve labeled *TT* shows the preference of shareholders for risk versus return. It is also upward sloping, since shareholders of an organization will presumably accept increased risk only if it is accompanied by an increase in expected returns. For convenience, it is drawn as a straight line, which effectively embodies the idea that shareholders' risk aversion is constant. To keep [figure 1.1](#) simple, only two such lines are drawn. What is important to understand is that the welfare of shareholders unambiguously increases as they attain higher *TT* lines. For example, any position along the line labeled *T'T'* is worse from the shareholders' perspective than any position on *TT*, because the shareholder is either accepting lower rates of return for the same risk along *T'T'* than along *TT*, or they are accepting more risk for the same rate of return.

The firm portrayed in [figure 1.1](#) is assumed to be representative of the population of private-sector firms in the economy. Furthermore, it is assumed initially that all citizens are also shareholders, so that the private-sector returns

6. Cromer, Dibrell, and Craig (2011) provide some support for this assumption by showing that the relative number of patent citations a company receives is positively related to that company's market value. The relevant notion here is that patents are an indicator of technological novelty.

7. These are essentially the assumptions underlying the capital asset-pricing model applied to financial investments.

Figure 1.1: Risk-Return Equilibrium



to innovation equal the social returns to innovation. It is also assumed that the representative firm fully internalizes the financial gains from innovation. The “equilibrium” for the representative firm is given by the tangency between the RR and TT functions, that is, at point e , corresponding to points P^1 and S^1 on the two axes. At the tangency point (e), the expected payoff at the margin for assuming additional risk is equal to the expected payoff required to assume additional risk from innovation. From the perspective of the shareholders of the representative firm, and therefore from the standpoint of society given our earlier assumption, an innovation strategy lying to the left of the vertical line drawn from the tangency point to the horizontal axis would be too “conservative”. That is, shareholders would prefer an innovation strategy involving greater attempts at novelty (and higher expected returns) with concomitantly greater risk. An innovation strategy lying to the right of the vertical perpendicular line would be too “radical”, that is, the associated increased risk is more than shareholders would prefer given the expected returns. An equivalent way of reaching this conclusion is to note that point e is a tangency between the TT line and the RR curve. This means that any position on the RR curve other than point e would move shareholders down to a lower TT line. As noted above, shareholders are better off when they are positioned on higher TT lines, that is, they have more risk-adjusted wealth.

Risk aversion of managers

The stylized equilibrium for the representative organization summarized in figure 1.1 helps identify the potential for market failure in allocating resources to private-sector innovation. Specifically, it helps identify the conditions that might lead to too much (or too little) incremental innovation from a social welfare perspective. One possibility in this regard is that the representative

organization fails to allocate resources efficiently. Specifically, it fails to choose the innovation portfolio having the optimal level of risk shown as S^1 in figure 1.1. The relevant concept that has been raised in this regard is that managers, particularly in large organizations, fail to act in the shareholders' interests, and favour incremental innovation unduly because it is in their "comfort zone" where measurement is easy and return on investment is predictable (Sviokla, 2014). In this context, private-sector managers may systematically fail to choose the socially efficient innovation strategy identified as S^1P^1 but, rather, will likely choose strategies that involve too much incremental innovation. That is, the organization will wind up in a position to the left of S^1 which would, in turn, mean that shareholders would not be on the TT line but on a lower line.

The argument that managers pursue their own self-interests and not the interests of shareholders is long-standing and has received much attention in the literature.⁸ The specific application of this argument to innovation activities has received relatively limited attention in the literature, so both theory and relevant evidence bearing on the claim that managers are "excessively" risk averse is reviewed in a later section of this essay.

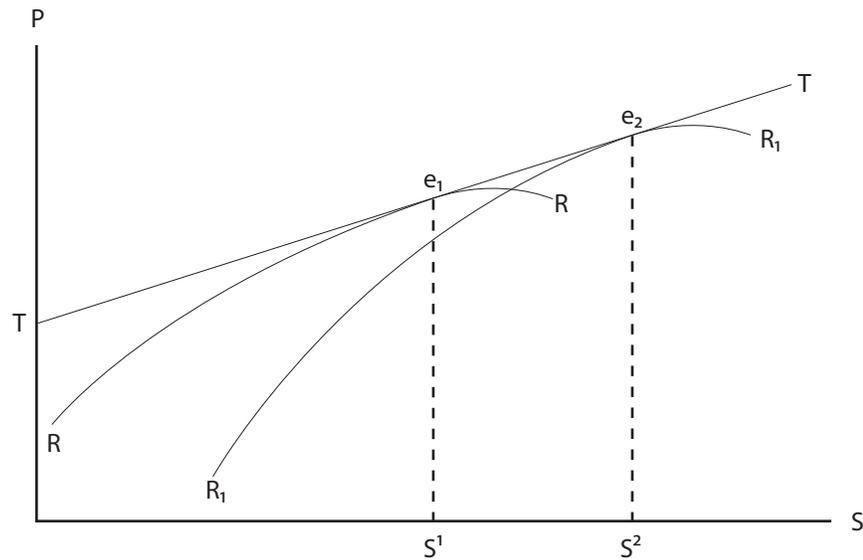
Spillover benefits to innovation

A second potential source of excessive incremental innovation relative to breakthrough innovation arises if we allow for some of the financial benefits of innovation to be captured by participants in the economy other than the innovating organization. This might arise either because some participants in the economy are not necessarily shareholders of innovating organizations and/or because individual innovating organizations cannot capture all of the financial benefits from their innovations. With respect to the latter possibility, numerous empirical studies document the phenomenon whereby innovation activities of individual organizations convey "spillover" technical or commercial benefits to other organizations in the economy (see, e.g., Bernstein, 1988). The existence of such spillovers underlies a general argument that private markets will produce "too little" innovation from a social welfare perspective in the absence of public policies to encourage innovation. In the context of the socially efficient mix of innovations, if the relevant spillovers are disproportionately large for more novel innovations, it can be argued that the representative private-sector firm will do too much incremental innovation and too little breakthrough innovation from the perspective of the economy as a whole.

The implications of the technology spillover phenomenon can be incorporated in figure 1.2 by showing a new R function (R_1R_1) that lies below the original function (RR) for relatively less risky innovation portfolios but lies above the RR function for more risky innovation portfolios. The basic idea here is

8. For a discussion of this potential phenomenon and a review of the relevant literature, see Czarnitzki and Kraft, 2004.

Figure 1.2: Risk-Return Equilibrium with “Spillovers”



that the presence of spillover benefits means that the expected incremental returns from any given increase in innovation risk will be greater for society as a whole than for any individual firm, but this is assumed to be true only for relatively risky (or breakthrough) innovations.⁹ Assuming that the risk-return preferences of society are the same as those of individual shareholders, (that is, that the TT function is unchanged), the new equilibrium (e_2) lies to the right of the old equilibrium (e_1). Equivalently, the preferred risk level for society associated with innovation (S^2) will be greater than the preferred risk level of the shareholders of the representative firm in the economy (S^1).

Summary

In summary, the claim that private-sector organizations acting independently will do too much incremental innovation can be related to two main arguments. One is that private-sector managers do not act in the interests of their shareholders and, specifically, that they are more risk averse when it comes to innovation than shareholders would prefer. A second is that technological spillovers particularly associated with breakthrough innovations result in private-sector organizations doing more incremental innovation relative to radical innovation than society as a whole would consider optimal. The rest of this essay considers these arguments in more detail and also discusses evidence bearing upon their relevance.

9. In fact, the social returns to innovation of all types are likely to be greater than their private returns. Figure 1.2 suggests that the social returns lie below the private returns for less risky innovations. This condition as represented by R_1 lying below R for a portion of the movement along the S axis is purely to facilitate a clear graphical representation of the potential market-failure phenomenon outlined in this paragraph.

4. Managers as agents for innovation

In an earlier section of this essay, it was noted that private-sector organizations may do too much incremental innovation if managers typically view themselves benefiting more from pursuing relatively routine goals for R&D and innovation than from pursuing relatively risky innovation projects. As noted, the stylized explanation in support of this premise is that managers of incumbent firms prefer the “quiet life”, whenever possible, and undertaking relatively risky technology programs is inconsistent with the quiet life.¹⁰ As a consequence, incumbents allegedly succumb to what Chandy and Tellis (2000) label the “incumbent curse”. That is, rigid attitudes toward change often result in the incumbent’s demise.

To be sure, incentive systems within organizations may discourage managers from taking risks that are warranted (from the shareholders’ perspective) by the expected returns. For example, if the compensation of senior managers largely consists of salaries, risk-taking will be discouraged, since compensation to managers would be largely unaffected at the margin by successful risk-taking, whereas unsuccessful risk-taking might result in losing one’s job. On the other hand, to the extent that managerial compensation is highly responsive to the future growth and profitability of the organization, managers would benefit from significant innovations and presumably would have strong incentives to pursue them. Indeed, one can conjecture a set of high-powered incentives that result in managers undertaking “too much” radical innovation from the shareholders’ perspective. In short, there is no *a priori* reason to believe that the incentives of managers of private-sector companies necessarily lead them to be excessively risk averse from the perspective of shareholders and, therefore, to do more incremental innovation than is consistent with profit-maximizing behaviour.

Another ubiquitous argument in support of the hypothesis that organizations “over-invest” in incremental innovation focuses on large, incumbent firms. For such organizations, it is argued that radical innovations will “cannibalize” sales of existing products or lead to a very rapid depreciation of existing machinery and equipment, depending upon the nature of the innovation. At the margin, therefore, according to this argument, incumbent firms will find radical innovation less profitable than will new, “entrepreneurial” firms, since the economic gains from radical innovation come partially at the expense of foregone sales of existing products, or the accelerated economic obsolescence of existing plant and equipment in the case of incumbent firms (Chandy and Tellis, 2000).

As Henderson (1993) and others point out, while incumbent firms may not like the idea of accelerating the economic obsolescence of existing products

10. The management literature characterizes such behaviour as “managerial rigidity”. See, for example, McKinley, Latham and Braun, 2014.

and physical capital, they may have little choice but to do so, in the absence of meaningful barriers to the entry of new firms. The alternative to avoiding cannibalizing existing products and production capacity might be an even more severe financial loss, even bankruptcy, brought about by other firms introducing radical innovations. In this regard, Henderson's interviews of managers in the photolithographic alignment equipment industry suggest that fear of product cannibalization was not a constraint in the formulation of established firms' product-development strategies. To be sure, numerous examples can be cited of individual products that were introduced by non-incumbent firms. At the same time, evidence from cross-section studies (discussed below) shows that incumbent firms are as likely to introduce radical innovations as new firms.

A somewhat different hypothesis maintains that incumbent firms might have the incentive to invest in radical innovation, but they do not have the requisite organizational structure and "culture" to do so successfully. Simply put, managers of incumbent firms, particularly large firms, are plagued by inertia which, in turn, discourages radical innovation.¹¹ The basic idea here is that radical innovation requires thinking "outside the box", and the capability and willingness to do so is allegedly blunted by the administratively determined practices and procedures characteristic of large, incumbent organizations (Baumol, 2004). In effect, organizations follow routines and procedures that may blind them to new products and processes that require different routines and procedures to be implemented (Hannon and Freeman, 1975). At the same time, there are organizational features that can help incumbent firms overcome organizational inertia. One notable example is the use of "skunk works", relatively small entrepreneurial units located within large organizations that have an executive mandate to develop and champion innovations that are radical for their company. Infusing younger workers into incumbent organizations can also encourage openness to radical innovation.

If large, incumbent organizations that account for the bulk of R&D done in developed countries have certain disadvantages when it comes to initiating radical innovation, they also enjoy potential advantages. For one thing, large organizations enjoy some risk diversification from the multiple projects they carry on, because these projects' outcomes are likely to be imperfectly correlated. The existence of risk diversification suggests that it is ordinarily less risky for large firms to add relatively ambitious innovation projects to their innovation portfolios than it is for small firms that may often face bankruptcy risks if technologically or commercially "ambitious" innovations fail to pay off. For another, the internal cash flows generated by large, incumbent firms can be a lower-cost source of financing than external capital that small, entrepreneurial firms need to raise from, say, venture capital companies. This should encourage large, established firms to undertake some innovation projects with relatively

11. This argument is made by numerous authors. For one example, see McLaughlin, Bessant and, Smart, 2005.

long payback periods. In this regard, Petkantchin (2012) argues that incremental pharmaceutical innovations ensure income continuity for drug companies that end up financing radical innovation.

In summary, it has been argued that large, established organizations will do too much incremental innovation, either because managers of those organizations are excessively risk averse, or because large organizations suffer from specific competitive disadvantages when it comes to undertaking breakthrough innovations. Notwithstanding the ubiquity of the arguments, they are theoretically unconvincing, since plausible arguments can also be made that large, incumbent organizations attempting to maximize profits may get close to the efficient mix of breakthrough compared to incremental innovation.

Studies document the availability of organizational arrangements that facilitate radical innovation in large, incumbent organizations when the expected risk-adjusted returns to such innovation are favourable (see, e.g., Ettl, Bridges, and O’Keefe, 1984). However, the empirical evidence on the extent to which established firms emphasize incremental as opposed to breakthrough innovation is sparse and not very conclusive, in part because classifying the degree to which innovations are incremental is a subjective exercise. As well, institutional differences across countries, such as the depth of venture capital markets, lead to findings that vary with the nationalities of the companies studied. Nevertheless, at least one study of some 64 innovations identified as “radical” by industry experts found that incumbents are as likely as non-incumbents to introduce radical innovations. Furthermore, large incumbents seem to have an advantage in introducing radical innovations compared to small and medium-sized incumbents (Chandy and Tellis, 2000).

5. The externalities from incremental innovation

As noted earlier, private-sector organizations might undertake too much incremental innovation from a social welfare perspective if breakthrough innovations convey technological spillovers on other organizations in the domestic economy, while incremental innovations convey few, if any, such externalities.

There is ample evidence in the literature that innovations, on the whole, have external economic benefits. That is, innovations introduced by organizations often lead to productivity improvements captured by other organizations without the initial innovator being compensated for the knowledge transfers that underlie the relevant spillover efficiency benefits. Furthermore, there is no doubt that major innovations such as the electrical light, the jet engine, and air conditioning, to mention a few cited by Gordon, have benefited society by a vastly larger magnitude than the economic gains realized by the early innovators of those products. What should be noted in this regard, however, is that major innovations are relatively rare compared to incremental innovations. Hence, to the extent that there are spillover benefits from incremental innovations, the aggregate commercial value of those spillover benefits might exceed the

commercial value of the spillovers to radical innovations, since incremental innovations are more numerous. In the next section, empirical evidence is reviewed bearing upon the spillover benefits of incremental innovation.

The spillover benefits of incremental innovation

Economic historians document the widespread and important spillover benefits that typically arise from incremental innovation. For example, innovation-induced qualitative changes in product characteristics often give rise to a train of responsive innovations in one or more of the successive stages of production reaching from raw-material producers to manufacturers of final consumer goods (Gold, Rosseger and Boylan, Jr., 1980). The innovations undertaken in other stages of the product's value chain would, in many cases, arguably not have been undertaken absent the initial innovation-induced changes to the product in question. A similar argument can be made for new production processes. Hence, even incremental product or process innovations in one stage of a value chain ordinarily promote innovation in other stages of the value chain, and the original innovator is unlikely to capture more than a modest share of the commercial benefits of further upstream and downstream innovations.

Consumers (industrial and household) are likely to be the major long-run beneficiaries of innovation, since they will enjoy access to improved products at prices that will incompletely reflect the commercial value of the improvements embodied in the innovations, as well as "standard" products at progressively lower prices. Simply put, consumers derive improvements in their economic welfare from acquiring products whose value to them exceeds the cost to them. This is a manifestation of technology spillovers captured by consumers.

Incremental innovations also play a prominent indirect role in the technology spillover process by making radical innovations adoptable by a wide range of potential users. Those who champion the importance of breakthrough innovations often implicitly and inappropriately equate the technological novelty of a new product or production process with its economic benefits. In fact, the economic significance of innovations does not necessarily depend on their technological originality.¹² Moreover, bringing an invention to the point of technical feasibility or workability is very different from establishing its economic superiority over existing techniques. The latter is accomplished by improving the invention's performance characteristics, often in very inconspicuous and unspectacular ways that increase the population of potential users, as well as the economic benefits those users derive. Rosenberg (1976) notes that the increases in the population of potential users, as well as the benefits that they derive from usage, are typically promoted by incremental improvements to the innovation in question.

12. Rayna and Striuka (2009) assert that there are numerous examples of incremental innovation influencing an industry in more significant ways than radical innovation.

The steel industry provides some prominent illustrations of this theme. The basic oxygen furnace (BOF) and the process of continuously casting molten steel are two processes hailed as “major” technological advances in the industry. In the case of both innovations, it took incremental changes in the original version of the innovation to make them commercially beneficial for a wide range of users. Although the BOF was seemingly a self-contained technology, its performance in a given setting depended on complementary changes made by producers in earlier and later stages of the industry’s value chain.¹³ Rosenberg (1976) provides additional examples of an important innovation that required complementary changes in order to be economically beneficial. One is the jet engine, which suffered from unacceptably low performance characteristics until materials were made available to withstand high temperatures and pressures.

More recent innovations reinforce the claim that extremely valuable new products are not necessarily technologically novel. For example, Rayna and Striukova (2009) argue that Apple’s most commercially successful products, including the iPod® and the iPhone®, represent incremental technological improvements rather than what might be categorized as radical innovation. Likewise, MS DOS and its successor (Windows™), as well as Google’s search engine, are also, in their opinion, incremental technological developments. Yin (1994) compares the financial returns from an initial radical process innovation to the returns from incremental changes to petroleum refining processes. He finds that incremental improvements generated higher returns than did initial radical innovations. Among many other additional examples that can be cited, Gelijns and Rosenberg (1994) document how medical instruments incorporating relatively modest technological improvements have facilitated major improvements in health-care practices with attendant benefits to patients.

Learning by doing

Incremental innovation can also promote radical innovation through the learning from earlier vintages of technology that innovators can profit from. Specifically, innovation builds upon earlier innovations which, in turn, promotes and directs technological change in the future. Numerous scholars make this argument. For example, Paul David (1975) highlights the importance of technological learning by doing as an important influence on what is learned by producers in the future. Specifically, production experience about what to produce and, especially, about how to produce it using presently known methods governs what subsequently comes to be learned. A dramatic illustration of this phenomenon is provided by Edison’s introduction of the incandescent lamp. While Edison introduced what was clearly a drastically new technical product, he also deliberately patterned many of his practices upon those of the old gas industry (see Passer, 1953).

13. For a detailed discussion of the BOF and continuous casting innovations, see Gold, Rosseger and Boylan, Jr., 1980.

There is substantial empirical evidence that incremental innovations provide significant learning-by-doing benefits both to the innovating organization as well as to other organizations. More generally, building innovation capabilities is a complex process that evolves slowly over time. Awate, Larsen and Mudambi (2012) document this phenomenon in their study of the wind turbine industry. They explain how a series of incremental innovations led to Danish wind turbines eventually being scaled up to meet broad commercial demand. Furthermore, the technological innovations of the industry leader (Vestas) were copied fairly rapidly and effectively by other producers. Vestas' patents also influenced innovations in several other industries that are not directly related to wind turbines. It is worth emphasizing that the Danish turbine evolved primarily through incremental innovation rather than radical innovation. Indeed, it proved commercially superior to its American "high-technology" counterpart. A second example is Sony's continual introduction of new Walkman™ and Discman™ models. Those models embodied incremental improvements in the underlying knowledge of the technology of personal tape recorders and CD players (see Helfat and Raubitschek, 2000). Another illustration is provided by Canon whose "revolutionary" 35mm camera drew on the company's core knowledge of precision optics and mechanics drawn from its experience making photocopiers.

Summary

Perhaps it is conventional wisdom that breakthrough or radically novel innovations convey large externality benefits on domestic economies, besides being profitable for the innovating organizations, while the externality benefits of incremental innovations are quite modest. If so, this conventional wisdom is not supported by available evidence. Specifically, the economy-wide cumulative benefits of incremental innovations may be just as great as, if not greater than, the economy-wide benefits of radical innovation.

6. Conclusions

Relatively slow rates of economic growth in developed economies over the past two decades have led some observers to call for a change in private-sector innovation strategies. Specifically, they are calling for a greater emphasis to be placed on breakthrough or radical innovation with less emphasis on incremental innovation. Public policies have primarily focused on encouraging more innovation without necessarily making explicit distinctions among different types of innovation.¹⁴ An exception in this regard is pharmaceuticals. In this sector, government regulators have been increasingly reluctant to sanction the sale of drugs that are not new therapeutics but, rather, modifications of established therapeutics.

14. Patent laws of most countries require some minimum degree of technical novelty for an invention to receive patent protection.

Lybecker's accompanying essay addresses the issues surrounding public policies toward incremental innovation in the pharmaceutical industry. This essay addresses the more general concern that private-sector firms are doing too much incremental innovation relative to breakthrough innovation. Two specific arguments are identified and evaluated. One is that managers are excessively risk-averse when it comes to innovation. A second is that the well-documented spillover efficiency benefits from innovation are primarily the consequence of breakthrough innovations, while incremental innovations create limited spillover benefits.

With respect to the first argument, the risk aversion of managers will depend largely upon how they are compensated. If shareholders want managers to undertake more risky innovations, boards of directors can implement compensation schemes that strengthen managers' incentives to do so. It is often argued that such remedies are difficult to implement in the context of large, incumbent companies characterized by organizational inertia and the desire of managers to avoid "cannibalizing" existing successful products; however, empirical evidence does not provide any systematic support for this argument. As well, the available empirical evidence shows that incremental innovations have substantial productivity spillovers. It is incorrect, therefore, to argue that spillover benefits in total are necessarily greater for the relatively small number of breakthrough innovations than for the relatively large number of incremental innovations.

In summary, there is no support for a concern from a social welfare perspective that private-sector companies are doing too much incremental innovation and too little breakthrough innovation. Hence, policy makers should avoid either explicitly or implicitly discouraging incremental innovation when designing policies.

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Incremental Innovation in the Pharmaceutical Industry

Kristina M. Lybecker

The cumulative effect of numerous minor incremental innovations can sometimes be more transforming and have more economic impact than a few radical innovations of “technological breakthroughs.

The National Research Council, 1996¹

1. Introduction

Pharmaceutical innovation works for patients and for society, resulting in new medicines and cutting-edge therapies that enhance and extend life. It is an inherently dynamic process: one innovation builds on another and improvements draw from a long history of earlier technological advances. In 2012, 45 new drugs gained regulatory approval from the US FDA, the highest number since 1997. Currently there are 907 biologics, medicines, and vaccines in development, targeting more than 100 diseases (PhRMA, 2013). Much of this innovation can be considered incremental, resulting in so-called “me-too” or follow-on drugs. These are therapies that largely replicate the action of existing drugs.

Berndt, Cockburn, and Grepin (2006) effectively outline the different types of pharmaceutical innovations defined by the US FDA.

The US FDA classifies NDAs [New Drug Applications] into seven categories that correspond to markedly different types of innovation. These categories are: (1) New Molecular Entity (NME); (2) New Salt of Previously Approved Drug;² (3) New Formulation of Previously

Chapter 2 in Steven Globerman and Kristina M. Lybecker, *The Benefits of Incremental Innovation: Focus on the Pharmaceutical Industry*. © 2014 Fraser Institute <<http://www.fraserinstitute.org>>.

1. As cited in Wertheimer & Santella, 2005: 6.

2. That is, different salts that may be used in the production of an existing drug. For example, the patent application for Imatinib notes, “wherein the pharmaceutically acceptable salt of imatinib is a hydrochloride salt, a hydrobromide salt, an oxalate salt, a maleate salt, a fumarate salt, a mesylate salt, a besylate salt, a tosylate salt or a tartrate salt” (US patent application number PCT/IB2010/003418).

Approved Drug (not a new salt or new molecular entity); (4) New Combination of Two or More Drugs; (5) Already Marketed Drug Product – Duplication (i.e. new manufacturer); (6) New Indication (claim) for Already Marketed Drug (includes switch in marketing status from prescription-only to over-the-counter); and (7) Already Marketed Drug Product – No Previously Approved NDA. The FDA defines an NME as “a new drug product containing, as its active ingredient, a chemical substance marketed for the first time in the United States. (Berndt, Cockburn, and Grepin, 2006: 72)

Between 1990 and 2003, the Center for Drug Evaluation and Research (CDER) approved 1,171 New Drug Applications (NDAs). Of these, 399 (34%) were for new molecular entities (NMEs), while 769 (66%) were non-NMEs. In addition,

[t]o date, 47 percent of biologics regulated by FDA’s Center for Drug Evaluation and Research have at least one new FDA-approved indication after the initial approval. Moreover, biologics that have been on the market for more than six years continue to generate new indications, and trials for new indications are ongoing for biologics approved ten or more years ago. (PhRMA, 2007: 3)

All indicators suggest that the majority of medical progress is happening through incremental innovation.

This study examines the value of incremental innovation in the pharmaceutical industry. Admittedly, it is difficult to draw the line between improvement technologies of doubtful validity and legitimate innovative advances. This is starkly evident in the disparity of opinions held by a large number of knowledgeable scholars and experts. It is essential to examine the value of incremental innovation and weigh the costs of providing patent protection for these advances. Ultimately, the intellectual property rights (IPRs) should balance the incentives for innovation against the market exclusivity that patents guarantee. At its worst, the critics are right and incremental innovation is solely a strategy to delay generic entry through secondary patents on originator compounds. At its best, these research endeavours allow for greater medical knowledge and improved treatments. Intellectual property policy makers should aspire to find a balance and then provide incentives to make it a reality. This study seeks to inform these issues. The remainder of the paper is structured as follows: Section 2 describes the different types of innovation; Section 3 considers the value of incremental innovation in the pharmaceutical industry; Section 4 outlines a number of fallacies surrounding incremental innovation and provides evidence to show that they are indeed fallacies; Section 5 examines several threats to incremental innovation; Section 6 provides specific examples of incremental innovations in pharmaceuticals; Section 7 concludes.

2. Types of innovation

Sir Isaac Newton once stated, “If I have seen far, it is by standing on the shoulders of giants.” In her classic paper on innovation, Scotchmer (1991) cites this quotation and emphasizes that virtually all technical progress builds on a foundation provided by earlier innovators. Innovation is an undeniably cumulative event, and progress happens both in leaps and bounds and in small steps. As noted in the essay by Globerman (2014) that accompanies this one, the literature distinguishes between different types of innovation in a number of ways, most notably through the extent of novelty. An extensive literature distinguishes between radical and incremental innovation. As described by Henderson (1993), radical innovation makes earlier technology obsolete, while incremental innovation amounts to an expansion of existing knowledge. In like manner, Baumol (2004) defines revolutionary innovation as truly novel and incremental advances as marginal extensions. In the context of the pharmaceutical industry, radical innovations encompass breakthrough discoveries of the “first-in-class” medicine with a new mechanism of action. In contrast, incremental innovations may expand an existing therapeutic class through the development of a new drug based on differences in adverse effects, delivery systems, dosing schedules, or heat stability.

3. Value of incremental innovation

Incremental pharmaceutical innovation is valuable to both patients and society, for both health and cost-saving reasons. This section describes a wide variety of benefits that accrue to us from such improvements. While the most obvious is the therapeutic benefit that comes from advances in medicine and incremental improvements to original advances, patients also benefit from being able to choose among a collection of alternatives within a single therapeutic class. This allows physicians to treat individual patients with sophistication, focusing on the convenience of specific dosing regimens or the elimination of particularly onerous adverse effects. Such choices also improve patient compliance, which enhances health outcomes. Not surprisingly, the first-in-class medicine, the first or breakthrough drug in a new therapeutic class, is rarely optimal or best-in-class. Through incremental innovations, researchers can “build a better mouse-trap” and the superiority of successive generations of some drugs attests to the benefits of this work. These efforts may also result in supplemental indications and the ability to treat unrelated conditions with the originator drug.

From an economic perspective, alternative therapies developed through incremental improvements increase the security of a reliable supply, safeguarding patient health in case other drugs within the therapeutic class are withdrawn from the market. Therapeutic alternatives also compete with original drugs, which drives down prices and, over time, has reduced the period of market exclusivity of the originator compound. The drugs resulting from these lines of research also generate overall healthcare cost savings. Moreover, incremental

innovations provide the lion's share of revenue of innovative firms, guaranteeing the continuation of breakthrough research programs. Finally, all innovation, including incremental innovation, is good for economic growth and development. The value of incremental innovation extends beyond patients to the global community, through enhanced health outcomes and economic progress.

3a. Therapeutic value

The therapeutic value of incremental innovation is perhaps most obvious in the prominence of these drugs on the World Health Organization's Essential Drug List (WHO EDL). The World Health Organization's EDL comprises those drugs deemed to be essential to address the public health needs of developing nations. They constitute a model formulary of the most basic drugs needed to alleviate developing country health needs. As described by the WHO:

Essential medicines are those that satisfy the priority health care needs of a nation's population. They are selected with regard to public health relevance, evidence on safety and efficacy, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the patient or community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility. (WHO, 1999)

The global acceptance of the WHO's Essential Drug List attests to the medical and public-health significance of the EDL, and the importance of these incremental advances. A recent study by Cohen and Kaitin (2008) finds that 63% of the drugs on the World Health Organization's Essential Drug Lists are follow-on drugs. Moreover, "nearly one-quarter of the therapeutic indications described by the WHO essential drug list are treated by drugs originally indicated to treat some other disease or condition" (Wastila et al., 1989: 114). These numbers speak to the importance of incremental innovation for meeting public health needs and improving health outcomes on a global scale.

3b. Importance of therapeutic alternatives

There is tremendous individual variation in patient response to, and tolerance of, any particular drug. Incremental innovation provides physicians with the flexibility to precisely treat the individual needs of diverse patients. Therapeutic alternatives within the same drug class may differ in their metabolism, molecule, regimen, dosing schedules, speed of action, delivery system, adverse effects, therapeutic profile and/or interactions. Specifically, incremental innovation increases the number of available dosing options, uncovers new physiological interactions

of known medicines, encourages children's compliance through reformulations, increases the shelf-life or heat-stability of a given medicine to ensure effectiveness in diverse environments, expands the number of treatment options available, improves patient administration, allows for the elimination of treatment-limiting drug reactions or side effects, and offers significant options to patients with different physiologic and pathophysiologic status (Wertheimer, Levy, and O'Connor, 2001; IFPMA, 2013; Cohen and Kaitin, 2008; Frishman, 1987; and others).

As noted by Wertheimer and Santella (2005), beyond the significant therapeutic value of a given drug, a precarious network of factors affects the drug's effectiveness. Advances in the area of drug delivery systems and dosage forms provide the ability to sustain therapeutic drug levels in patients for ever-longer periods of time, to control the drug's rate of absorption, to limit drug activity to a specific type of cell, and to reduce adverse reactions. Research into more effective and fine-tuned delivery systems has made possible transdermal delivery, controlled-onset, and extended-release formulations. These advances allow for "using smaller amounts of active agents, fewer doses, less invasive modes of administration" (Starr, 2000: 107).

The value of therapeutic alternatives is evident in the decisions made by the World Health Organization in updating the Essential Drug List. Cohen, Cabanilla, and Sosnow (2006) note the following examples: Ciprofloxacin, an anti-bacterial follow-on, was added in response to concerns of growing microbial resistance to older anti-bacterial drugs. Lopinavir/ritonavir, a follow-on combination HIV/AIDS drug, was added due to an improved safety and tolerability profile compared with the first-in-class drug, ritonavir.

Consider the development of multiple generations of beta-blockers. The different advantages of each are described below in [table 2.1](#). Of particular importance, the use of beta-blockers requires physicians to also take into account concurrent therapy with other agents:

Concurrent administration of beta blockers with drugs that alter gastric, hepatic, or renal function may affect blood levels, duration of action, or efficacy of beta-blocker action. The beta blockers vary in the extent to which their action is altered when they are given with other agents, and therapeutic substitution may produce unwanted side effects and toxicity. (Frishman, 1987: 1197)

Given the variety of other medications that are likely to be used by patients taking beta-blockers, different drugs will be best suited to different cohorts of patients.

3c. Enhanced compliance

The value of therapeutic alternatives is evident in their impact on patient compliance. With multiple therapeutic choices, patients are more likely to comply with their treatment regimen given that they can select their treatment based

Table 2.1: Advantages of selected beta-blockers

	Preserves blood flow to and from the kidneys	Once daily dosing*	Reduces mortality after heart attack	No change in blood cholesterol levels	Selectively targets B1 receptors	Equal effectiveness in blacks and whites	Possesses ISA-Intrinsic sympatho-mimetic activity	Very low central nervous system penetration	Relaxes blood vessels resulting in improved blood flow
Acebutolol		✓			✓		✓		
Atenolol		✓			✓			✓	
Labetalol	✓			✓		✓			✓
Metoprolol		✓	✓		✓				
Nadolol	✓	✓						✓	
Pindolol	✓			✓			✓		
Propranolol		✓	✓						
Timolol			✓					✓	

Note: * Once-a-day dosing: Metoprolol is once a day for hypertension and Propranolol is for controlled-releases delivery only.

Source: adapted from Frishman, 1987: 1193.

on simplified administration or minimization of the side effects: “Transdermal delivery, delayed-onset, and extended-release formulations have all contributed to patient compliance with treatment regimens” (IFPMA, 2013: 12). Compliance with treatment regimens is important to therapeutic success and improved health outcomes and both are more likely when physicians and their patients have more choices.

3d. First-in-class versus best-in-class

Moreover, the first-in-class drug is rarely best-in-class. Given this, incremental improvements after initial adoption are critical to both pharmaceutical and biological development (Gelijns and Rosenberg, 1994: 31). Subsequent development allows for improvements in a therapeutic class that would otherwise never occur. DiMasi and Paquette (2004) provide some perspective on the value of follow-on drugs by analyzing the priority rating they received from the US FDA during the approval process.³

Given that the first-in-class drug is already on the market treating a given condition with an acceptable risk/benefit ratio, it is probably fair to say

3. “Prior to approval, each drug marketed in the United States must go through a detailed FDA review process. In 1992, under the Prescription Drug User Act (PDUFA), FDA agreed to specific goals for improving the drug review time and created a two-tiered system of review times—*Standard Review* and *Priority Review*. A *Priority Review* designation means FDA’s goal is to take action on an application within 6 months (compared to 10 months under standard review)” (US FDA, 2013).

the US FDA is not generally much disposed to giving a priority rating for a new drug in the same class for what might be fairly modest improvements in convenience, safety profiles or efficacy. Nonetheless, we found that approximately one-third of all follow-on drugs have received a priority rating from the US FDA. In addition, 57% of all classes have at least one follow-on drug that received a priority rating. These values likely underestimate the extent to which the best-in-class drug is not the first-in-class, because, as noted above, it is unlikely that relatively minor improvements in an existing chemical or pharmacologic class will result in a priority rating from the US FDA. (DiMasi and Paquette, 2004: 8)

While first-in-class, breakthrough therapies are frequently afforded a priority rating, one would expect far fewer incremental innovations to also receive a priority rating. The evidence provided by DiMasi and Paquette establishes the value of many of these follow-on drugs, based on the evaluation of the US FDA.

3e. Supplemental indications

Medical researchers have long known that follow-on studies can reveal very important therapeutic uses, frequently for an indication unrelated to the initial disease condition. In a recent study by Berndt, Cockburn, and Grepin (2006), the authors analyzed data on three important classes of drugs,⁴ focusing on the share of drug utilization indications that differed from that specified in the initially approved labeling. They found this share to be very substantial in two of the three drug classes considered. Specifically, they found that for SSRI/SNRIs, more than 75% of total utilization has been prescribed for conditions other than the primary indication, and in the case of PPI/H₂-antagonists, the share was between 70% and 80% over the period considered. In contrast, for ACE inhibitors (*angiotensin-converting-enzyme inhibitors* are used primarily for the treatment of hypertension) the share of non-primary utilization is only 15%. While the authors do note that while these drug classes may not be fully representative of the pharmaceutical market, the results point to the importance of incremental innovation, which “may have significant benefits both for drug developers and for patients, since the incremental gains from supplementary indications may be large relative to the investments made for supplementary approvals” (Berndt, Cockburn, and Grepin, 2006: 81–82).

Admittedly, the research required for new indications often requires designing new clinical trials to test the safety and efficacy of the medicine for an additional use since the optimal dosing and formulation regimes may differ across indications. Follow-on research is less costly than developing new therapies, but still expensive. Firms must expect the financial rewards to cover

4. The classes included: ACE inhibitors, histamine H₂-antagonists/proton-pump inhibitors, and selective serotonin/norepinephrine reuptake inhibitors.

the additional development and clinical trial costs. Nevertheless, supplemental indications do provide “more bang for the R&D buck”. That is, rather than beginning with a new research agenda, supplemental indications build upon existing work, and the additional costs associated with their development is far less than the 12 years and US\$1.2 billion required to bring a new drug to market (DiMasi, Hansen, and Grabowski, 2003).

Beta-blockers currently have more than 20 different uses. A fraction of these are delineated in table 2.1 above. Beyond the therapeutic value of the originator drug, incremental innovations have expanded the range of uses for existing medicines. In addition, reformulation can result in valuable new applications for existing drugs. Wertheimer, Levy, and O’Connor (2001) describe many significant examples of reformulations in [table 2.2](#), below.

3f. Greater supply security

An additional advantage of the therapeutic alternatives resulting from incremental innovation is enhanced supply security. This is particularly important in the event of market withdrawals, shortages, and/or regulatory action. Wertheimer and Santella (2005) describe numerous cases in which the originator drug was removed from the market, increasing the use of the other drugs in the therapeutic class: “Examples include the antihistamines terfenadine and astemizole, the anti-inflammatory agents zomepirac, benoxaprofenm and suprofen, and the fluoroquinolone antibiotic grepafloxacin; all removed as a result of clinical results showing infrequent but severe side effects” (Wertheimer and Santella, 2005: 7) In each of these cases, the follow-on drugs provided an essential back-up for patients, while they may also be superior in some respect. For example, when dicumarol was recalled the World Health Organization replaced it on the Essential Drug List with warfarin, which was superior in safety, efficacy, and versatility (Cohen, Cabanilla, and Sosnov, 2006: 591).

3g. Increased price competition

In addition to the health benefits described above, incremental innovation in the pharmaceutical industry delivers cost savings. Critics argue that the development of follow-on or me-too drugs duplicates existing knowledge and wastes scarce R&D resources. Conversely, others claim that their production increases price competition and brings valuable alternatives to market. In fact, one of the principal advantages of the development of follow-on drugs is the price competition that results from multiple drugs in a single therapeutic class. DiMasi (2000) examined 20 new entrants to existing classes (1995–1999) and found that 80% were launched at a discount relative to the price leader and 65% were launched at a discount relative to the average price for the class. Further, the average percentage decrease in price was 26% relative to the price leader and 14% relative to the class average. The results of DiMasi’s (2000) study are shown in [table 2.3](#) below. DiMasi’s work demonstrates that incremental

Table 2.2: New formulations with extended uses

Drug	Original indication	New formulation	Extended uses
Antibiotics	Parenteral use only	Oral preparations Topical forms Inhaled use	Bowel preparation, hepatic coma Skin, eye, ear infections Cystic fibrosis
Corticosteroids	Steroid-responsive conditions	Intravenous bolus injections Enemas	Same use with greater efficacy and safety Ulcerative colitis
Cromolyn sodium	Prophylaxis of asthma by aerosol Eye drops	Nasal insufflation	Hay fever Hay fever
Glyceryl trinitrate	Angina	Transdermal patch	Greater efficacy
Heparin	Intravenous treatment for venous thrombosis	Subcutaneous low-dose	Prophylaxis of postoperative venous thrombosis
Medroxyprogesterone acetate	Endometriosis, etc.	Depot injection	Long-term contraception
Morphine	Pain	Slow-release injection Epidural injection	Prolonged action Regional analgesia
Pilocarpine	Glaucoma	"Ocuserts"	Prolonged action
Vancomycin	Parenteral antibiotic	Oil-paste (Matrigel) capsules	Antibiotic-induced pseudomembranous colitis

Source: Wertheimer, Levy, and O'Connor, 2001: 85; modified from Snell, 1986.

innovation delivers cost savings, as well as therapeutic choice, to patients. In an age of escalating medical costs, increased price competition and the lower launch prices it generates convey significant savings to patients and insurers.

3h. Reduced Period of Market Exclusivity

Agarwal and Gort (2001) studied the period of market exclusivity that innovators enjoyed over the period from 1887 to 1986 for a wide selection of industries. They demonstrate that the speed of entry following the launch of an innovation has increased dramatically over time. At the turn of the twentieth century, the mean time to entry was 33 years; this fell to less than 3.5 years over the period extending from 1967 to 1986. In the context of pharmaceutical innovation, a study by DiMasi and Paquette (2004) examines trends in the rate at which competing products enter the pharmaceutical marketplace and the competitive nature of the development process. They analyze 72 drug classes in which the first-in-class compound was approved between 1960 and 1998, finding 235 follow-on drugs approved through 2003.

While the literature on speed to entry in the pharmaceutical industry is sparse, several studies have found that the mean time to entry is decreasing (Kettler, 1998; Towse and Leighton, 1999; DiMasi and Paquette, 2004). DiMasi

Table 2.3: New drugs in existing classes tend to be priced at a discount

Subclass	Brand name	Launch month, year	Discount relative to weighted mean price (%)	Discount relative to price leader (%)
ACE inhibitors	Univasc	May 1995	52.7	67.8
	Mavik	June 1996	30.4	53.2
ARBs	Diovan	February 1997	1.4	1.4
	Avapro	October 1997	-2.6	-2.6
	Atacand	October 1998	0.3	0.3
	Micardis	December 1998	0.7	0.7
CCBs	Sular	February 1996	37.7	67.9
	Posicor	July 1997	80.8	55.0
COX-2 inhibitors	Vioxx	May 1999	0.0	0.0
Macrolides	Dynabae	October 1995	42.6	49.0
Non-sedating antihistamines	Allegra	August 1996	14.1	15.0
PPIs	Prevacid	May 1995	10.1	10.1
	Aciphex	September 1999	4.9	6.7
Statins	Lipitor	January 1997	33.9	60.1
	Baycol	January 1998	29.5	43.1
SNRIs	Serzone	February 1995	9.7	9.7
SSRIs	Luvox	January 1995	8.1	12.7
	Celexa	August 1998	17.9	23.0
Third-generation cephalosporins	Cedax	February 1996	-7.4	20.0
	Omnicef	August 1998	-3.1	18.2

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; COX-2 = cyclooxygenase-2; PPI = proton pump inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

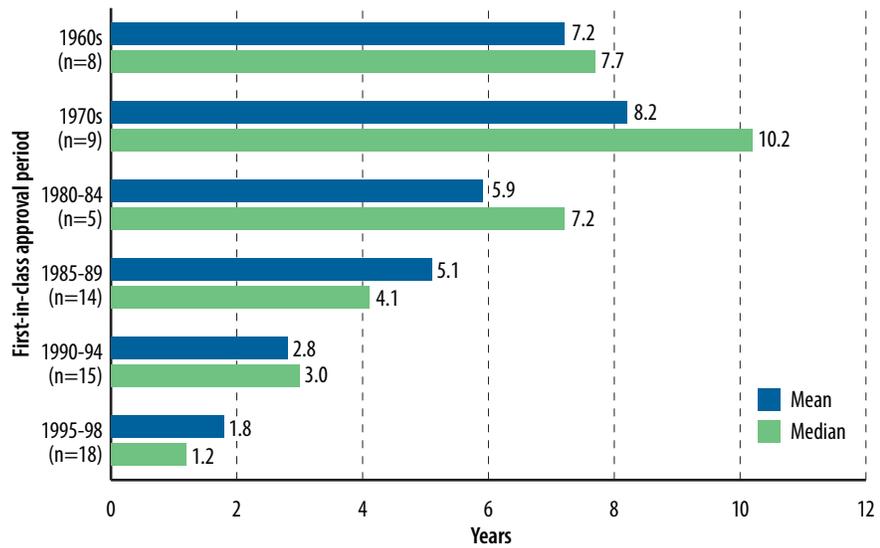
Note: A positive value indicates a lower price for the new entrant, while a negative value indicates a higher price.

Source: Wertheimer & Santella, 2005: 12, citing DiMasi, 2000.

and Paquette find that the period of market exclusivity decreased over the period studied. The mean length of the period of market exclusivity fell from 8.2 years in the 1970s to 1.8 years in the period from 1995 to 1998, a decrease of 78% (DiMasi and Paquette, 2004: 5). **Figure 2.1** below plots the average period of marketing exclusivity for first entrants in a therapeutic class, calculating the time from first-in-class approval to the first follow-on drug approval.

Greater investment in incremental innovation has increased the number of alternative therapies available, increased price competition and dramatically decreased the period of market exclusivity enjoyed by originator therapies. Each of these conveys benefits to consumers, lowering healthcare costs and

Figure 2.1: Average period of marketing exclusivity



Source: DiMasi and Paquette, 2004: 5.

providing therapeutic choice to patients. The reduced period of marketing exclusivity corresponds to efficient market incentives and greater competition.

3i. Overall health savings

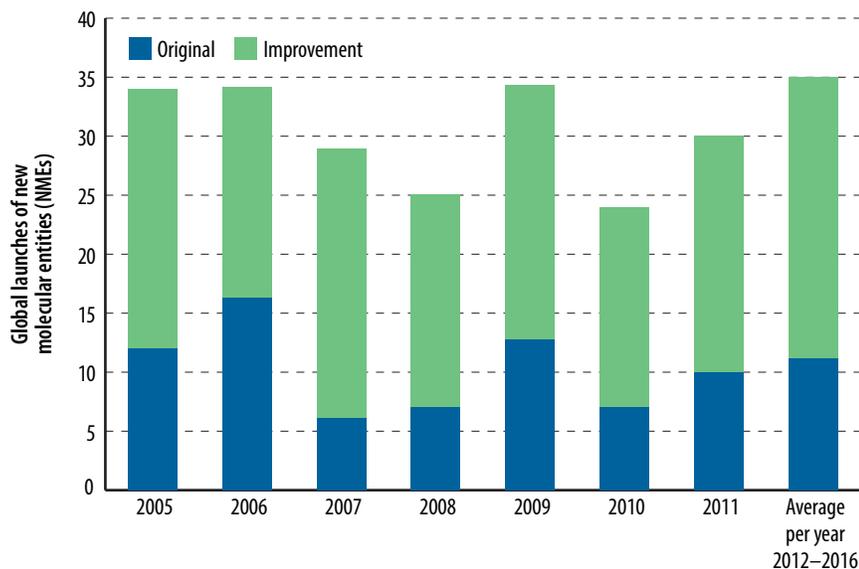
Pharmaceutical innovation, including incremental pharmaceutical innovation, also reduces overall healthcare costs. According to a 1996 study, a \$1 increase in pharmaceutical expenditure is associated with a \$3.65 reduction in hospital care expenditure (Lichtenberg, 1996). In the case of incremental innovation specifically, Wertheimer and Santella (2005) provide a valuable perspective, nothing that while “it is unrealistic to presume that every incremental innovation leads to cost savings, the sum of all drug innovations can result in cost savings in the following areas: reduced overall treatment costs; shortened or eliminated hospital stays; increased worker productivity and less absenteeism; reduced drug costs from increased competition among manufacturers” (Wertheimer and Santella, 2005: 10). For example, the costs to the US economy of hay fever and its associated absenteeism and diminished worker productivity are estimated to total between US\$2.4 and US\$4.6 billion, annually, due to the sedating effects of antihistamine medications. Accordingly, the development of non-sedating antihistamines can be expected to reduce these costs significantly (White and Case, 2009; Wertheimer, Levy, and O’Connor, 2001).

3j. Financial necessity

Incremental innovation is a financial necessity for high-tech industries such as biotechnology and pharmaceuticals. Given the paucity and unpredictability of radical innovation, incremental advances sustain the industry financially, for no mature industry can do so from income derived from breakthrough innovation

alone. As described by Wertheimer, Levy, and O'Connor, “[t]he pharmaceutical industry must generate revenue based predominantly on incremental innovations, which characterize the majority of products and contribute the majority of revenue” (Wertheimer, Levy, and O'Connor, 2001: 108–109). Evidence of the prevalence of breakthrough relative to incremental innovations is shown in **figure 2.2** below. Over the entire period, products based on incremental innovations outnumber breakthrough products. In addition, it is essential to recognize the importance of risk management. Any technology portfolio will comprise projects of differing risk levels. In the case of the pharmaceutical industry, incremental innovation projects are an essential—and significant—component of this portfolio. The incremental innovation projects will be characterized by lower risk and a greater probability of reaching the market (Wertheimer, Levy, and O'Connor, 2001: 110).

Figure 2.2: Relative number of first-in-class and incremental products



Source: based on IFPMA, 2013: 11, fig. 3.

3k. Innovation is good for growth

Finally, protecting innovation fosters economic growth and development, and that includes incremental innovation. A growing body of empirical evidence demonstrates that increasingly robust intellectual property protections, in combination with other policies, increase economic development, foreign direct investment (FDI), and innovation.⁵ A 2006 report from the United

5. An excellent review of this literature is provided by Pugatch, Torstensson, and Chu (2012). Their study documents the findings of more than 40 studies that demonstrate the positive correlation between intellectual property rights, foreign direct investment, trade, and economic development. These studies examine both industrialized and developing nations from all regions of the globe, demonstrating that as intellectual property rights are strengthened economic growth ensues.

Nations Industrial Development Organization (UNIDO) studied the role of intellectual property rights in advanced nations in technology transfer and economic growth, concluding that protecting innovation creates benefits for countries at all levels of development. For developing countries, strengthening intellectual property rights encourages growth. For middle-income countries, evidence indicates that domestic innovation and diffusion of technology can lead to growth and that strengthening IPRs can encourage industries to shift from imitation to innovation. For advanced economies, stronger IPRs increase innovation and raise growth (Falvy, Foster, and Memedovic, 2006). Moreover, enforcing intellectual property rights and protecting innovation also drives research on cures. This is true of the diseases of both industrialized and developing nations. A recent study by Kyle and McGahan (2012) finds evidence of more research on diseases in nations with TRIPS-compliant IP provisions, as their patent provisions were put into place and implemented, than on diseases prevalent in non-TRIPS-compliant nations, controlling for the level of economic development and other factors.⁶

For example, although India only represents about 1% of the global pharmaceutical market, innovation is nonetheless valuable to India and other nations in the developing world. Following the adoption of the IP protections in the TRIPS Agreement, research and development in India increased by 20% (Pugatch, Torstensson, and Chu, 2012). Even in a market as small as India, stronger intellectual property rights encourage innovation and foster growth. This linkage is further documented in a growing body of empirical evidence that demonstrates that stronger intellectual property protections, in combination with other policies, increase economic development, foreign direct investment (FDI), and innovation. (Lybecker, 2013)

4. Fallacies surrounding incremental innovation

Incremental innovation, especially in the pharmaceutical industry, has more than its share of critics. Their arguments largely focus on the supposedly duplicative nature of follow-on research, waste of resources, and abuse of the patent system, criticisms that fall apart upon deeper examination. This section focuses on dispelling a number of the fallacies that surround incremental innovation.

6. The World Trade Organization's (WTO) Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) is the most comprehensive international agreement on intellectual property to date, codifying minimum standards for many forms of intellectual property protection for WTO Members. Negotiated in 1994, at the end of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT), the TRIPS agreement marked the first time intellectual-property law appeared in an international trade agreement. Following concerns that the Agreement could pose a threat to public health, the 2001 Doha Declaration clarifies the scope of TRIPS, providing that TRIPS can and should be interpreted in light of the goal "to promote access to medicines for all". For additional information, please see the World Trade Organization's website, <http://www.wto.org/english/thewto_e/thewto_e.htm>.

4a. The patents protecting incremental innovations are not legitimate patents

The primary criticism of incremental innovation is that the patents are not legitimate because the innovations are supposedly insufficiently novel and, therefore, the innovator companies are abusing the patent system. In fact, when incremental innovations are awarded patents, it is because they are valid and well deserved. The criteria for patentability, for all fields of technology and whether product or process, require that an innovation be novel, non-obvious, and useful. That is, the invention was not previously known, it is inventive in some way, and it is capable of commercial application. Patent law does not distinguish between breakthrough discoveries and incremental innovations; they are both patentable if the legal criteria are met. It is also worth noting that incremental innovations are patented by innovator firms as well as other firms and even by generic producers. For example, Lamictal was originally developed as an anticonvulsant to treat epilepsy by GlaxoSmithKline (GSK). Subsequent research by GSK led to the development of a dispersible tablet that simplified use and compliance. The success of the dispersible table prompted several generic producers to “design around” the GSK patent, and several competing versions are now on the market (GSK, 2011a).

While critics contend that patents comprising “mere” new uses of known compounds or new delivery systems should not be patentable, patents are awarded only after being assessed by trained patent examiners and deemed to meet the legal standards for patentability. Moreover, further review takes place if required by a legal challenge. When the validity of a patent comes into question, the courts step in. Worthy innovations are defended and where patents have been wrongly granted, the legal system should, and typically does, remedy those errors.

4b. Incremental innovation represents duplicative research efforts and offers little value

Two critics contend, “85-90% of new products over the past 50 years have provided few benefits and considerable harms” (Light and Lexchin, 2012: 4). Another critic writes, “the share of investments in new products that have significant improvements over existing treatments is 20 percent, with 80 percent of the investment in new products spent on projects that demonstrate no significant improvement over marketed products” (Love, 2003: 18). Such critics believe that new products should be mandated to provide evidence of “medical value”, the drug’s relative effectiveness (in comparison to other drugs), and therapeutic superiority. The consequences of this mandate would be dire and likely reduce innovative research efforts. Such “medical value” arguments are particularly problematic because much of the research done on what turn out to be follow-on drugs is done before a single drug is approved in the class, making studies of comparative effectiveness an expensive afterthought and increasing

the risk of drug development. Specifically, innovators would have to do the impossible: demonstrating a product's superiority to drugs that are simultaneously being developed and are not yet on the market. DiMasi and Paquette (2004) provide an excellent rebuttal of the "medical value" argument and the challenges and risks associated with insisting pharmaceutical innovators measure their performance relative to a moving target.⁷

The development of multiple medicines in existing classes has led to the perception that the pharmaceutical industry is overly focused on so-called me-too drugs that offer little additional value over existing treatments. "This position is misguided. It shows a lack of understanding of scientific processes, and ignores the fact that most pharmaceutical R&D is incremental—indeed, incremental innovation is the key to most major advances in the treatment and prevention of disease" (GSK, 2011b). The evolution of therapeutic treatments is built upon the small steps and therapeutic advances that incremental innovation provides. An extensive list of specific examples is provided in Section 6 below.

The value of incremental innovation may, in part, be demonstrated by the US FDA priority review classification they receive. DiMasi and Paquette examine the US FDA's priority ratings for new drug approvals. Their examination provides some perspective on the perceived value of these compounds. They describe the US FDA priority review system as follows:

The US FDA established a three-tiered rating system for prioritizing review of new drug applications in late 1975. New drugs thought at the time to represent a significant gain over existing therapy, a modest gain over existing therapy, and little or no gain over existing therapy were given an A, B, and C rating, respectively. The US FDA altered its rating system to a two-tiered one in 1992; since then, the US FDA rates new drugs as either priority (P) or standard (S). (DiMasi and Paquette, 2004: 4)

They find that 80% of the first-in-class drugs received a priority rating for regulatory review by the US FDA, and approximately one third of the follow-on drugs received a priority rating. Additionally, 57% of the therapeutic classes studied have at least one follow-on drug that received a priority rating. This suggests that incremental innovations provide valuable, frequently significant, gains. The priority rating indicates that such drugs demonstrated improvement over existing therapies in one or more ways: "(1) evidence of increased effectiveness in the diagnosis, treatment or prevention of a disease; (2) elimination

7. DiMasi and Paquette note that a "firm can start a development program in one way, only to find partway through it that it has to change course and do comprehensive head-to-head comparisons with a drug that happened to reach the marketplace before its drug. This can even happen more than once in development. That is, the firm would be required to hit a moving target. Such a policy may well increase uncertainty about future costs and the likelihood of approval to the point that no firm is willing to risk development in some areas" (DiMasi and Paquette, 2004: 13).

or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness for a new patient subpopulation” (White and Case, 2009: 6).

It is possible to measure the extent of the benefits of supplemental indications and incremental innovations, by quantifying the degree to which they incentivize spending on research and development. In estimates dating from around 2002, CMR International (2002) estimates that approximately 30% of R&D spending is devoted to line extensions,⁸ while Pharmaceutical Research and Manufacturers of America estimates that share to be about 18% (PhRMA, 2001). This investment occurs because of the potential financial gains that may accrue to the innovative firm. However, it is important to recognize that the gains are but a fraction of the benefits stemming from innovation. The lion’s share of the benefits to innovation are the spillover to society as a whole. Multiple studies establish that the rate of return to society from corporate research and development and other innovative activities is at least twice what the innovator receives.⁹

4c. Incremental innovation is merely post-hoc imitation

A number of recently released books (Angell, 2004; Avorn, 2004; Goozner, 2004) criticize the innovative pharmaceutical industry for their increasing investment in so-called “me-too” drugs that have a similar mechanism of action to pre-existing drugs. Critics argue that this is merely imitation and worth very little since the industry has failed to provide evidence of clinical benefits relative to pre-existing therapies.

In an examination of the speed to entry in 72 therapeutic classes, DiMasi and Paquette (2004) find that the majority of drug development on what turn out to be follow-on drugs takes place prior to the approval of the first-in-class approval. That is, rather than duplicative research and *post-hoc* imitation, it is more accurate to describe this as parallel drug development (DiMasi and Paquette, 2004: 8). As shown in [table 2.4](#) below, follow-on drugs were moving through every development phase prior to the first-in-class approval. That is, innovative firms were simultaneously pursuing research that resulted in therapies in a new therapeutic class.

Moreover, as shown in [figure 2.3](#), in a significant number of cases, the first-in-class drug to gain approval in the US market was not the first to enter clinical testing either in the US or any other jurisdiction (DiMasi and Paquette, 2004: 10). The share of follow-on drugs for which an Investigational New Drug Application (IND) was filed before the first-in-class compound is in the range of 9% to 38%. In addition, the share of follow-on drugs that were first tested in humans (globally anywhere) before the first-in-class compound was as high as 42% in the 1990-to-1994 period.

8. A line extension differs from an existing pharmaceutical product only in form or strength.

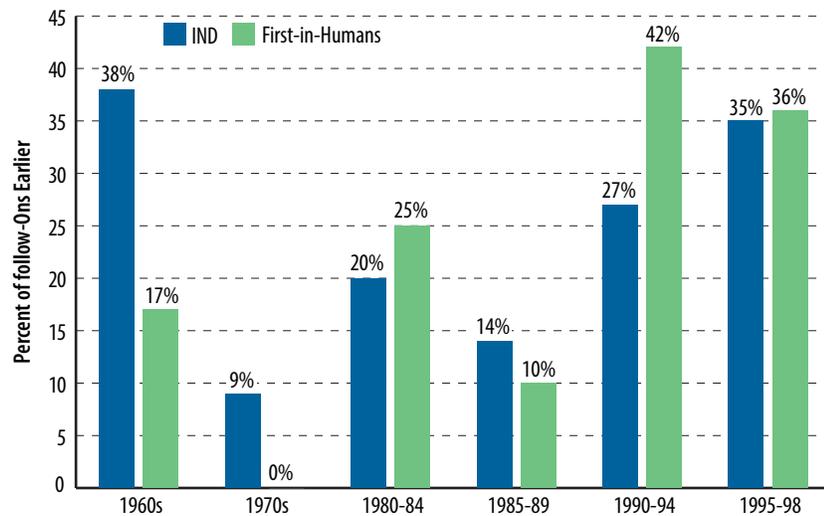
9. For example, see Mansfield, 1991, Jones and Williams, 1998, and Brynjolfsson, Hitt, and Yang, 2000.

Table 2.4: Share of follow-on drugs with development phase initiated prior to first-in-class approval, by period of first-in-class US approval

Development phase	Percentage (%) initiated prior to first-in-class approval					
	1960s	1970s	1980–84	1985–89	1990–94	1995–98
Synthesis	32 (n = 31)	45 (n = 22)	85 (n = 13)	100 (n = 15)	100 (n = 14)	100 (n = 12)
First pharmacological test	26 (n = 31)	43 (n = 21)	83 (n = 12)	75 (n = 20)	100 (n = 17)	93 (n = 15)
First in humans anywhere	17 (n = 42)	27 (n = 26)	50 (n = 16)	67 (n = 30)	92 (n = 24)	96 (n = 23)
IND filing	16 (n = 44)	16 (n = 31)	30 (n = 27)	55 (n = 47)	59 (n = 34)	85 (n = 34)
Phase II	3 (n = 34)	10 (n = 21)	31 (n = 16)	48 (n = 31)	75 (n = 16)	83 (n = 18)
Phase III	3 (n = 35)	13 (n = 24)	11 (n = 19)	39 (n = 31)	45 (n = 22)	67 (n = 21)

Source: DiMasi and Paquette, 2004: 10.

Figure 2.3: Percentage of follow-on drugs approved in the United States from 1960 to 2003 that were first tested in humans anywhere in the world or had an investigational new drug (IND) application filed prior to that for their first-in-class compound (for therapeutic classes where the first-in-class drug was approved in the US from 1960 to 1998)



Source: DiMasi and Paquette, 2004: 10.

DiMasi and Paquette (2004) provide significant evidence of the concurrent nature of the research programs that lead to the development of many follow-on drugs. While critics contend that profit motivates the development of imitation versions as firms race to get their me-too drugs to market, test data indicates that these research programs are better described as parallel drug development.

4d. Incremental innovation is really “evergreening” and a strategy to delay generic competition

The “evergreening” of pharmaceutical patents is a contentious issue at the intersection of intellectual property rights and public health. Critics maintain that through this strategy, the patenting of “minor” improvements, innovator firms are able to extend the period of market exclusivity and delay the introduction of generic competition. They argue that this then has a negative impact upon public health through higher prices and reduced access to medicines. The argument goes something like this: “Though patents are presumed to reward genuine inventions, lax rules on patentability and shortcomings in procedures permit protection to be obtained on a myriad of minor developments. These patents, though weak and possibly invalid in many cases, are used to restrain competition and delay the entry of generic competition” (Correa, 2004: 784). Advocates, on the other hand, assert that technological progress occurs incrementally and effective intellectual property policy provides for patents on improvement inventions. Moreover, when patents are erroneously awarded, legal challenges will arise to either confirm or deny the patent’s validity. The question then becomes: to what extent do secondary patents protect valid innovation, rather than serving to delay generic competition?

In a recent study of secondary patenting on two HIV drugs, Amin and Kesselheim examine the extent to which incremental improvement patents could extend market exclusivity for ritonavir (*Norvir*) and lopinavir/ritonavir (*Kaletra*). They identified 108 patents, one of which would not expire until 39 years after the first patents on ritonavir were filed. However, the majority of these “secondary patents” protect peripheral features. “In general, we found that most of the patents extending past the expiration date of patents on the original base compounds fell into the categories of polymorphs¹⁰ (lasting up to 2019 for ritonavir and 2021 for lopinavir); methods of use of the drugs; and formulation patents—in particular, the heat-stable tablet formulation” (Amin and Kesselheim, 2012: 2289) Notably, these patents do not protect the chemical compounds contained in these drugs and would not prevent generic production of the innovator drug upon the expiry of the original patents.

10. A polymorph is a specific crystalline form of a compound that can crystallize.

Nevertheless, additional research has shown that secondary patents do have an effect on the market exclusivity of innovative drugs, potentially adding several years to the effective patent life.

For drugs that have chemical compound patents, secondary patents add on average between 4 and 5 years of additional nominal patent term. Drugs that do not have chemical compound patents rely much more substantially on secondary patents for exclusivity: here, when there are secondary patents, they generate an average of 9 and 11 years of patent term beyond the standard data exclusivity period. (Kapczynski, Park, and Sampat, 2012: 6–7)

Kapczynski, Park, and Sampat also find that the propensity of innovative pharmaceutical firms to seek secondary patents after drug approval increases over the sales distribution. This may indicate that firms deliberately attempt to extend protection for their most lucrative products.

Then again, it is essential to recognize that by design the patent system allows for the production of generic versions of the basic product, following the expiration of the patent on the original compound. That is, patents associated with a medicine based on subsequent incremental innovation of an existing medicine do not affect the patent term for that originator medicine because the two patents are independent. Accordingly, following the expiration of the original patent, generic versions are able to compete in the market with the improved product, protected by the so-called “secondary” patent(s).

Once the patent exclusivity period of the existing medicine expires, any firm, regardless of the patenting activity related to a subsequent improvement, may begin to produce and market that medicine so long as appropriate regulatory requirements are met. Thereafter, only patient needs will determine whether there is a demand for the subsequent improved medicine. (IFPMA, 2013: 6)

However, it is worth acknowledging that secondary patents complicate the minefield of existing intellectual property rights that competitor firms must navigate when endeavouring to bring a generic to market. More generally, “[c]oncern about non-innovative secondary patents in pharmaceuticals reflects a broader one, across industries, that resource constrained patent offices may be issuing a large number of low quality patents, i.e. patents that would not have been granted if subjected to proper scrutiny” (Kapczynski, Park, and Sampat, 2012: 2). Moreover, it is important to acknowledge that the onus of sifting through the collection of patents does fall on the generic manufacturer who hopes to introduce a competing product. As noted by several studies (Hemphill and Sampat, 2011; Amin and Kesselheim, 2012), this may lead to

litigation and could increase the costs faced by generic producers. That said, there are costs borne by the innovator firms as well. In a recent article in *Science*, Higgins and Graham (2009) describe their concern that the rise in challenges shortens effective market life, thereby reducing the return on investment and the incentives to innovate. It may be that this has contributed to the frequently observed dearth of new branded drugs. This generic strategy of increasing patent challenges has been termed, “prospecting” (Hemphill and Sampat, 2012: 327, citing use by Higgins and Graham, 2009 and Grabowski and Kyle, 2007;) The increased litigation over pharmaceutical patents has undeniably affected both innovator and generic firms, but the true consequences are most felt by patients.

Although critics maintain that through evergreening innovator firms are able to extend the period of market exclusivity and delay the introduction of generic competition, advocates assert that technological progress occurs incrementally and effective intellectual property policy provides for patents on improvement inventions. While research has shown that secondary patents may have an effect on the market exclusivity of innovative drugs, it is essential to recognize that by design the patent system nevertheless allows for the production of generic versions of the basic product, following the expiration of the patent on the original compound. Accordingly, patient needs will ultimately determine if the subsequent improved medicine is valued by the market and finds sufficient demand.

4e. Incremental innovation diverts research resources from work on neglected diseases

Finally, critics argue that incremental innovation takes resources away from more innovative work or research that is needed on neglected diseases: “Third-world health-advocacy organizations ... contend that such ‘me-too’ and ‘follow-on’ research yields drugs with little or no therapeutic value over innovative drugs and that underdeveloped nations suffer from this insignificant research” (Wastila et al., 1989: 105). This line of thinking is frequently accompanied by an argument advocating weakened patent protection, especially for developing nations, and/or the denial of patent protection for incremental innovation. In a recent article in the *New England Journal of Medicine*, Amy Kapczynski makes just such an argument: “Provisions like Section 3(d) can help reverse this effect [prioritizing incremental innovation over breakthrough drug discovery] and encourage companies to undertake the riskier and more expensive research that is required to generate breakthrough drugs” (Kapczynski, 2013). This position is strikingly naïve. It is difficult to imagine how weaker intellectual property rights (IPR) protection will give innovative pharmaceutical firms an incentive to expend more resources and take on greater risk, especially for the treatments needed in developing nations. The economics of innovation suggest just the opposite. Stronger intellectual property protection encourages innovation, increasing the probability the innovator will realize

a return on the tremendous investment of time, talent, and financial resources required. Through a stronger IP paradigm, innovative firms are encouraged to take on risk and invest scarce resources.

Contrary to Kapczynski's interpretation, enhanced IPRs foster valuable pharmaceutical innovation and speed the development of breakthrough therapies (Lybecker, 2013). This conclusion is echoed in the work of Kyle and McGahan (2012) who found that protecting innovation enhances research on cures, rather than inhibiting it. Their work finds evidence of more research on diseases in nations with TRIPS-compliant IP provisions as patent provisions were implemented than on diseases in non-TRIPS-compliant nations (Kyle and McGahan, 2012). Implementing protections for innovation, including incremental innovation, generates the research that results in life-enhancing and life-extending treatments.

5. Threats to incremental innovation

This study has already argued for the value of incremental innovation and described the benefits it confers on patients, firms, and society. This section focuses on those elements that threaten incremental innovation, touching on a negative legal landscape, challenges to balancing portfolio risk, and recent changes in the international intellectual-property climate. Each of these poses a challenge to continued incremental innovation, and the costs and benefits of any policy change should be viewed with cautious scepticism.

5a. Litigation

All innovation is sensitive to the legal environment, the political climate, and rumours of what is on the horizon. Pharmaceutical innovation is risky, difficult, and expensive. Additional risk, therefore, especially an unfavourable change in the legal environment, can greatly affect the incentives for conducting pharmaceutical R&D. The increased risk of financial losses created by litigation will reduce the incentives to invest in innovation, even incremental improvements. Historically, this is evident in the cases of childhood vaccines¹¹ and contraceptives (Peck and Rabin, 1990; Calfee, 2007; Wertheimer, Levy, and O'Connor, 2001).

5b. Inability to balance portfolio risk

As described above, incremental innovation provides critical funding for entire research programs, including those encompassing breakthrough research. The inability to protect incremental innovation will remove the incentives to invest in those projects and could undermine entire research programs. As noted by Kettler, "companies are also better able to balance their portfolio risk if they combine lower risk, incremental innovation projects with projects geared to

11. As Calfee (2007) notes, innovation on childhood vaccines virtually dried up due to abusive lawsuits until those preventative were moved out of the tort liability system in 1986.

produce breakthroughs” (Wertheimer, Levy, and O’Conner, 2001: 78, citing Kettler, 1998). The importance of revenue generated by incremental innovations is evident in the numbers: “New drug products based on incremental pharmaceutical innovations accounted for about \$17 billion or about 38% of all new spending in the retail prescription drug market” (White and Case, 2009: 6).

5c. Changes in the international intellectual property protection climate

Perhaps the most significant challenge to incremental innovation lies in the shifting patent landscape of developing nations. While the most significant changes are taking place in India, industry observers worry that there may be a contagion effect undermining pharmaceutical innovation in other nations such as China, Russia, Brazil, and South Africa. Notably, in the past two years India has invalidated or otherwise attacked the pharmaceutical patents held by international firms (Hunter, 2014). Of particular concern is Section 3(d) of the Indian Patent Act, which forbids the patenting of new forms of known drugs unless the new form significantly enhances efficacy and yields therapeutic benefits. Accordingly, much of the incremental innovation that is done on existing treatments will no longer be patentable under this interpretation.

In an analysis of Section 3(d), Abbott (2013) describes the main points made by the Indian Supreme Court in a recent case against drug maker Novartis as including the following:

1. ... Section 3(d) was proposed by the Government with the stated purpose of addressing concerns raised by members of Parliament that the introduction of pharmaceutical product patent protection would substantially inhibit the availability of medicines for the population of India and developing countries more generally. Parliament sought to limit practices that might result in the grant of patents for insubstantial technological contributions. Parliament adopted in the Section 3(d) amendment, including the explanation, a requirement that patents for new forms of known substances should only be granted on the showing of a significant enhancement in known efficacy.
2. International legal rules accepted by India, in particular the WTO TRIPS Agreement, provide sufficient leeway or flexibility in the adoption of patenting standards to allow the approach adopted by the Indian Parliament.
- ...
8. The Supreme Court interpreted the meaning of “efficacy” in Section 3(d). It said that the new form of a drug must demonstrate an improvement in its therapeutic effect of curative property as compared to the old form in order to secure a patent. (Abbott, 2013)

First, this interpretation removes the incentive for improvements to existing therapies. Second, incremental innovation is critical to the developing world. Incremental innovations provide for more convenient extended-release dosing and formulations that do not require refrigeration or are less temperature sensitive, valuable characteristics in developing-country settings. As noted earlier in this study, follow-on drugs are an important share of the World Health Organization's Essential Drug List. Follow-on drugs comprise 63% of the EDL, which points to their value and importance to public health and development efforts (Cohen, Cabanilla, and Sosnov, 2006). Moreover, follow-on drugs are becoming more important over time as this share has increased more than 25% over the previous two decades. Finally, the Indian Patent Office is now bound by the interpretation of "increased efficacy" as therapeutic efficacy. Given this, it is important to ask how the threshold for "therapeutic benefit" will be defined. The ambiguity surrounding how this requirement will be interpreted increases the risk and uncertainty of innovation and will reduce the incentives for future innovation (Lybecker, 2013).

Fundamentally, the Gleevec case (*Novartis AG vs. Union of India*) amounts to an interpretation of Section 3(d) of Indian patent law, clarifying what does and does not constitute a patentable invention. The patent application that Novartis provided for Gleevec contended that Gleevec is absorbed more quickly and has greater stability than the original drug. Novartis also claimed novelty, inventiveness, and industrial applicability, thereby satisfying the necessary patentability requirements. In its decision, the Indian Supreme Court denied Novartis a patent for Gleevec because "the mere change of form with properties inherent to that form would not qualify as 'enhancement of efficacy' of a known substance" under section 3(d) of the Indian Patents Act 2005 (*Novartis AG vs. Union of India*, Supreme Court of India, Civil Appeal Nos. 2706-2716 of 201, 1 April 2013, pg. 91)" (Kilday, 2013). Ranjit Shahani, Vice Chairman and Managing Director of Novartis India, responded to the ruling by stating, "We should be more worried about what impact this will have on patient well-being and the ability to address the challenge of unmet medical needs." Even after pharmaceutical patent protection became law in India, Shahani notes that China has attracted billions of R&D investments made by seven global pharmaceutical companies (Novartis, Roche, Sanofi, Pfizer, GSK, Astra Zeneca, and Eli Lilly), and not a single investment came to India, which "speaks loudly about the innovation ecosystem we have here" (Chatterjee, 2013). Companies elect to conduct their pharmaceutical research and development in nations where their IP rights are protected and enforced, safeguarding their investments. Clearly Mr. Shahani recognizes the importance of strong intellectual property rights to economic growth and development. Unfortunately, the recent interpretation of Indian Patent Law and the possibility that it may be replicated by other nations have the potential to undermine not only innovation, but also economic progress across the developing world.

6. Examples of incremental innovations in pharmaceuticals

All innovation is valuable to the economy and to patients, whether in the form of breakthrough discoveries or in the form of incremental innovations. The earlier sections in this paper describe, in detail, the tremendous value of incremental innovation, both in the case of follow-on medicines as well as new uses for existing therapies, so-called supplemental indications. Beyond this, it is important to recognize that the majority of existing therapies currently in use are incremental innovations. To illustrate the importance of such improvements, it is valuable to consider specific examples and the manner in which they have improved health outcomes for patients. The list below is but a small sample of valuable incremental innovations improving health and extending lives today. Given that those who most vehemently oppose protection for incremental innovations frequently cite the need for treatments for neglected diseases and maladies of the developing world, it is important to note that many of the treatments described below have specific application to neglected diseases and the maladies of the developing world.

AIDS: Efavirenz/emtricitabine/tenofovir DF, the first-ever single-pill AIDS treatment regimen combining three drugs into one pill, simplifying the dosing regimen and increasing patient compliance. (Cohen and Kaitin, 2008: 90)

AIDS-related Kaposi's sarcoma: Both daunorubicin and doxorubicin, which are used to treat AIDS-related Kaposi's sarcoma, are delivered in liposome delivery systems, which reduces toxicity and concentrates the drug in areas of infection. (Wertheimer, Levy and O'Connor, 2001: 84)

Antibiotic-resistant bacterial infections: Structural modifications have produced successive generations of drugs in multiple families: penicillins, quinolones, aminoglycosides, and cephalosporins. Moreover, successive generations are often effective against a broader spectrum of bacteria. (Wertheimer, Levy, and O'Connor, 2001: 90)

Bacterial infection: Modifications of the original version, penicillin G, allowed for greater oral effectiveness, longer half-life, and resistance to inactivation by staph bacteria. (Taurel, 2004: 4)

Cancer: Rituximab was originally approved for the treatment of cancer, but was later found to treat rheumatoid arthritis. (Calfee, 2007: 2)

Cardiovascular therapy: The adoption of controlled-release formulations of anti-hypertension drugs has resulted in greater efficacy, safety, and compliance. (Wertheimer and Santella 2005: 11)

Chagas disease: Clinical trials are underway to explore the effects of the anti-fungal medicine ravuconazole against the pathogen that causes Chagas disease, a neglected tropical disease affecting nearly 10 million people. (IFPMA, 2013: 14)

Chronic myeloid leukemia: Dasatinib was the first in the next generation of imatinib-related drugs. (Cohen and Kaitin, 2008: 90–91)

Colorectal cancer: Bevacizumab was initially approved to treat colorectal cancer and has since been shown to be effective against certain lung cancers, breast cancer, and possibly kidney cancer. It is being investigated in some 20 clinical trials against different cancers or stages of cancer. (Calfee, 2007: 2–3)

Congestive heart failure: Captopril was the first ACE (angiotensin converting enzyme) inhibitor. Unpleasant side effects led to additional research efforts that yielded a completely new understanding of the enzyme linked to congestive heart failure. (IFPMA, 2013)

Contraception: Use of the first generation of oral contraceptives in the early 1960s increased the risk for thromboembolic disorders. Subsequent research resulted in the development of pills with lower doses of estrogen, which dramatically reduced the side effects. (Gelijns and Rosenberg, 1994: 31)

Crohn's disease: Infliximab was initially approved for the treatment of rheumatoid arthritis, but was then found to treat Crohn's disease. (Calfee, 2007: 2)

Diabetes: Inhaled insulin administered through an inhaler has been shown to have a more rapid onset of action than injected insulin. (Cohen and Kaitin, 2008: 90)

Early-stage breast cancer: The new indication of trastuzumab has shown beneficial effects on recurrence rates and mortality. (Cohen and Kaitin, 2008: 91)

Haemophilia: Derived from plasma, Factor VIII treats haemophilia, and through continued R&D efforts numerous improvements have resulted in much higher purity. (International Chamber of Commerce, 2005: 10)

Hay fever/allergies: First generation antihistamines had anticholinergic effects (such as dry mouth) and also produced driving impairment similar to that produced by alcohol. New antihistamines, such as *Allegra*, retain the activity of earlier compounds but have improved tolerability, reduced side effects, and enhanced safety. (Wertheimer, Levy, and O'Connor 2001: 87)

Hepatitis C virus: A modified formulation of interferon alfa (IFN α) improved the positive response rate of patients receiving treatment from 38%–43% to 54%–56% and drastically simplified dosing regimens, improving patient compliance. Peginterferon alfa-2a is administered only once a week, compared to the three to seven weekly doses needed by patients on a regimen of conventional IFN α . (IFPMA, 2013: 19, 21)

Malaria: Improvement innovation led to the development of a new formulation of two anti-malarial drugs, artesunate and amodiaquine, reducing dosing regimens from eight tablets a day to two. (IFPMA, 2013)

Psoriasis: Etanercept was originally approved for the treatment of rheumatoid arthritis, but was then found to treat psoriasis. (Calfee, 2007: 2)

Strokes: Atorvastatin was originally approved as an effective cholesterol-reducing drug, but has since been shown to prevent strokes. (Calfee, 2007: 3)

Type-2 diabetes: The combination of two treatments, metformin and saxagliptin, allows for a single dosage form, a much simpler drug therapy regimen. (IFPMA, 2013)

This list brings the value of incremental innovation into stark focus. Considering these examples of incremental innovations, it is clear that there is significant value for patients from the development of such treatments and therapies. Moreover, it is frequently through these incremental improvements that medicines are adapted to conditions found in developing countries. For example, they can provide an increase in the shelf-life or heat-stability of a given medicine to ensure effectiveness in diverse environments or adjust the drug's delivery mechanism to allow for easier administration by untrained, non-medical personnel.¹² As noted by the World Intellectual Property Secretariat, “many follow-on and patented innovations might contribute in a positive way to the improvement of public health and also to economic development, and ... some forms of adaptive innovation may be especially relevant to meeting neglected health needs” (WIPO, 2005: 19)

12. For example, ritonavir is a first-line treatment of HIV/AIDS. Approved by FDA in 1996, the original medicine required refrigeration, making its treatment less accessible in developing countries lacking widespread refrigeration. Then, in 2010, a heat-stable version was introduced, greatly improving access for patients in developing countries. In addition, a 1998 patent awarded to two Los Alamos National Laboratory bio-engineering researchers, Mark Bitensky and Tatsuro Yoshida, allows for the preservation of red blood-cell quality and prolongs post-transfusion *in vivo* survival by depleting the oxygen in the blood at the time of storage, significantly increasing the shelf-life of donated blood (Mascheroni, 2008).

7. Conclusions

All innovation is valuable and worth protecting, therapeutic breakthroughs as well incremental advances. These innovations provide the medicines that extend and enhance life. As described in this study, innovation is good for patients, good for growth, and good for economic development. The scientific and financial resources required for these advances are an investment worth making and an important precedent for global health. Moreover, since “drug therapy is generally agreed to be the most cost-effective treatment modality, the economic stakes are high” (Wertheimer, Levy, and O’Connor 2001: 112). Accordingly, policy makers should be particularly wary of any restrictive policies that exclude incremental innovation from intellectual property protection.

This study provides an evaluation of incremental pharmaceutical innovation and makes the case for supporting and rewarding such advances. Failure to do so would undermine the incentives for pharmaceutical incremental innovation to the detriment of global public health. Attesting to the therapeutic value of these innovations, a recent study finds that 63% of the drugs on the World Health Organization’s Essential Drug Lists are follow-on drugs, and close to one quarter of the therapeutic indications described are treated by drugs initially indicated to treat a different disease or condition.

Beyond the therapeutic value these drugs provide, the choice that they offer physicians and their patients is also of great value. As described earlier, incremental innovation provides physicians with the flexibility to treat the individual needs of diverse patients with precision. Therapeutic alternatives within the same drug class may differ in their metabolism, molecule, regimen, dosing schedules, speed of action, delivery system, adverse effects, therapeutic profile and/or interactions. In addition, incremental innovation increases the number of available dosing options, uncovers new physiological interactions of known medicines, encourages children’s compliance through reformulations, increases the shelf-life or heat-stability of a given medicine to ensure effectiveness in diverse environments, expands the number of treatment options available, improves patient administration, allows for the elimination of treatment-limiting drug reactions or side effects, and offers significant options to patients with different physiologic and pathophysiologic status. While increasing the number of treatment options available to patients is a primary goal of incremental innovation, it bestows other benefits as well. Incremental innovation generates price competition and overall savings in the healthcare arena.

While critics argue that incremental innovation represents a waste of resources and generates minor improvements, not worthy of patent protection, the evidence indicates that these criticisms do not withstand close scrutiny. Beyond the numbers, specific examples of incremental pharmaceutical

innovations illustrate the benefits patients receive. Each of the drugs described in the preceding section is valuable to those whose suffering they alleviate. It is essential to recognize the value of these treatments and those that will build upon them in the future. They must be protected, as must incentives for continued pharmaceutical R&D of both incremental and breakthrough products. The future of public health is at stake.

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