Public and Private Sector Contributions to the Research & Development of the Most Transformational Drugs of the Last 25 Years

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Executive Summary

Much has indeed changed in the paradigm by which biopharmaceutical R&D is conducted since the authors undertook their first analysis of the relative contributions of the public and private sectors to the discovery and development of new medicines nearly two decades ago. What has not changed is that when you examine the drugs that have contributed the most and are still contributing significantly to the health and well-being of the US and even globally, the role of the biopharmaceutical industry is pivotal in the translation from theory to therapy. In fact, two decades of reliable analyses by academia and government, assessed using a variety of methodological approaches, consistently demonstrate that 67 percent to 97 percent of drug development is conducted by the private sector.

In the current study, the authors examine a diverse array of evidentiary materials on the history of 19 individual drugs, 6 drug classes and 1 drug combination identified as the most transformative drugs in health care over the last 25 years by a survey of over 200 physicians conducted by two Harvard Medical School researchers. The results of the analysis show that drug discovery and development is anything but a direct linear process. Instead it is a complex ecosystem with a wide range of novel collaboration archetypes, involving industry-academic partnerships, venture capital, disease foundations, as well as public-private, pre-competitive consortia, so that learning is from many disciplines and the result of multiple feedback loops.

In fact, only 4 individual drugs appear to have been almost completely researched and developed by one sector, however, one sector or the other did dominate particular phases of the R&D continuum. For example, 54% of basic science milestones were achieved predominantly by the public sector, and 27% by the private sector. For discovery milestones, it was 15% by the public sector, and 58% by the private sector. The private sector was again dominant in achieving the major milestones for both the chemistry/manufacturing/controls and drug development phases, in 81% and 73% of the drugs reviewed, respectively. For 19-27% of the case histories in all categories, dominance of one sector versus the other could not be determined. The research that was done was expansive in its scope, often spanning oceans in the geographic reach of the institutions involved, as well as extending over decades, an average of 25 years from discovery to approval.

These drugs are having a positive and profound impact on healthcare even today. Nearly 70% of these drugs are now available as generics in the US, and are making contributions to medical systems worldwide. In fact, nearly 40% of the drugs appear on the World Health Organization (WHO) Model List of Essential Drugs – a list of some 300 drugs, which are therapeutically important, affordable and generally in ready supply in appropriate formulations. In addition, nearly 40% of the drugs have orphan indications, thereby providing therapy for rare disease populations, likely for unmet medical needs for which there were few, if any, treatment options. Almost all of these drugs have been launched on a worldwide basis and are still actively in development for additional indications or formulation improvements.

The results of our analysis confirm just how critical the private sector is to the time and resource consuming process of drug development. While the basic science underpinning the key disciplines...
Public/Private Sector R&D Contributions to the Most Transformational Drugs of the Last 25 Years

needed to discover and develop drugs is often initiated in academia, it is pharma firms, in particular, where these disciplines grow to give the necessary critical mass, expertise and experience needed for successful drug discovery. Disciplines like medicinal chemistry, process chemistry and formulation, drug metabolism and pharmacokinetics, and safety sciences are practiced at a scale and level of competence and integration in the industry that far outstretch academic applications.

But some remain skeptical of the role of the private sector in this important enterprise, and assert that it could and should be exclusively within control (at least financially) of the government. This begs the question: How Much Government Funding Would be Needed to Replace Industry New Drug R&D? In response, we made an effort to conservatively assess what the additional cost to government and taxpayers would be if such a radical policy change were made. To keep the analysis consistent with the period covered by the particular innovative compounds that we study in detail in this report, we initially restricted attention to new drugs approved from 1987 to 2002. The estimates suggest that conservatively the NIH budget would have to nearly double to maintain just the flow of the most innovative drug approvals, and would have to increase nearly two-and-half times to maintain the development of all new drugs. The relative inexperience of government in the latter stages of the R&D continuum would likely result in the government spending significantly more on developing new drugs than does the industry. We found even higher relative costs for drugs approved from 2003 to 2011. Given the trends for industry R&D costs and NIH budget appropriations, it is also likely that an analysis of more recent and future approvals would show more substantial increases in the relative cost of private sector R&D.

Far from being a bystander prior to marketing, industry’s scientific contributions go beyond drug development and include basic and applied science, discovery technologies, and manufacturing protocols. With available funding from the public sector decreasing while medical needs and scientific complexity increase, private sector collaborations with academia and government have become increasingly key in furthering medical advancement.
I. Introduction

In the 15 years since Tufts CSDD undertook its first in-depth review of the relative contribution of the public and private sectors to the research and development (R&D) of new medicines, much has changed. The funding available for biomedical R&D from the NIH has flat-lined, even decreased in relative terms, while the amount spent by the biopharmaceutical industry has doubled over the same time period (see Figure 1). The biotech revolution and demographic evolution of major pharmaceutical firms set in motion a paradigm shift in company structure and behavior that have created a 21st century biopharmaceutical industry bearing little resemblance to last century’s big pharma hegemony. What has not changed is that when you consider the drugs that have contributed most significantly to the health and well-being of the US and even globally, the role of the biopharmaceutical industry is pivotal in the translation from theory to therapy.

What has changed is that industry has implemented a wide range of novel collaboration archetypes in a unique approach combining inputs from industry-academic partnerships, venture capital, disease foundations, and public-private, pre-competitive consortia so that learning is from many disciplines and the result of multiple feedback loops. The cohort of drugs that we examined in the current study exhibited many instances of public-private interdependence, a feature of the evolving

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1 A Research & Development Ecosystem for the 21st Century, Pfizer Presentation, May 2, 2014
R&D paradigm that has become more pronounced over the last decade. The result was a medical armamentarium that was considered transformational for health care over the last quarter decade.

Thus it is particularly ironic that one of the major criticisms of the biopharmaceutical industry voiced in certain quarters is that companies within the industry take credit for inventing a product without having actually contributed to its creation. Although this fiction endures, it has never been proven true and is at odds with two decades of reliable analyses by academia and government based on sponsorship, patent, project, and licensing data, as well as considerations of central scientific contribution to applied science, clinical improvement, and the development of manufacturing protocols that consistently demonstrate 67 percent to 97 percent of drug development is conducted by the private sector.2,3,4,5,6,7 This fact in no way diminishes the public sector’s efforts in discovering innovative drugs and biologics; publicly funded research has been demonstrated to be vital for the advance of pharmaceutical science and improved medicines. Trends in R&D have been building throughout the last several decades that serve only to increase the interdependence of the two sectors, making it the prominent feature of the landscape for biomedical innovation in the 21st Century. Yet, the criticism persists that industry only buys up the hard work of others, repackages it, and sells it at a premium to the public who funded the work to begin with, adding little value to the process or the products along the way.

For years, critics have argued that important advances in medicine are a result of the efforts of public agencies. Publicly funded research is concentrated during the basic research phase. However, basic science is defined by the International Council of Science as “fundamental theoretical or experimental investigative research to advance knowledge without a specifically envisaged or immediately practical application.”8 In the life sciences, basic research might encompass exploration of the biology of a disease, that can identify a protein, a receptor, or an enzyme (i.e., drug targets) implicated in the disease. This is a critical step but still a long way from becoming a new medicine. While the basic science underpinning the key disciplines needed to discover and develop drugs is often initiated in academia, it is pharma firms, in particular, where these disciplines grow to give the necessary critical mass, expertise and experience needed for successful drug discovery.

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Disciplines like medicinal chemistry, process chemistry and formulation, drug metabolism and pharmacokinetics, and safety sciences are practiced at a scale and level of competence and integration in the industry that far outstretch academic applications. Technology innovation also occurs mainly in pharma’s domain. High throughput screening, parallel chemistry, structure-based drug design, and the large-scale measurement of \textit{in vitro} properties needed to design safe medicines with acceptable dosing frequency are capabilities not widely available in the academic setting, but which are de rigueur capabilities for private industry processes and practices.

Several recent studies have supported the premise that while the public sector is often responsible for laying the basic science groundwork, the private sector provides the kind of applied research and development needed to get drugs approved for marketing. According to Sampat & Lichtenburg, “government funding has an indirect role in drug development – funding basic underlying research that is then built upon.”\(^9\) In Stevens et al., the investigators make a distinction between the key contributions of the public and private sector in the R&D process of new medicines. This study describes public research contribution as “upstream,” meaning publicly funded research often provides insight for basic research, illuminates the mechanisms of a disease, as well as identifies pathways for therapeutic intervention. The private sector also contributes the basic science, but these contributions emerge more often during the later discovery stages for a specific product and succeeding stages of development that are necessary to bring those drugs to launch (which the researchers define as “downstream”).\(^10\) Stevens et al. explain how the industry has evolved over the last few decades due to the emergence of biotechnology companies and major policy changes in the 1980s. The passing of the Bayh-Dole Act in 1980 allowed universities, nonprofit research institutes, and teaching hospitals to own intellectual property and then have the ability to license those findings to whomever they chose (including private companies). Thus, a new system emerged in which the two sectors worked together to translate scientific findings into real products that can be marketed.\(^11,12\)

By looking closely at the development of some of the most innovative drugs of the last fifty years, researchers have begun to understand just how interdependent the innovative process for new medicines has become. This was amply demonstrated by the current authors in their prior work in conjunction with economist Ben Zycher from the Center for Medical Progress. That paper discusses the relative contributions to the R&D of 35 important drugs by the public and private sector in three crucial stages: basic science; applied science; as well as clinical, delivery and manufacturing improvement.\(^13\) It found that the central scientific contribution by the private sector was evident in all categories, but most significantly to applied science, followed closely by its contribution to enhancing clinical performance and improving commercial production. Nonetheless, the authors

\(^9\) See Sampat & Lichtenburg at 4  
\(^10\) See Stevens et al at 5  
\(^11\) Reichert JM, Milne CP. Public and private sector contributions to the discovery and development of “impact” drugs. \textit{American Journal of Therapeutics.} 2002; 9(6): 543-555  
\(^12\) See Stevens et al. (2011)  
\(^13\) See Zycher, DiMasi, and Milne (2008) at 3
acknowledge that the importance of publicly funded research cannot be downplayed, but that both sectors are crucial for advances in pharmaceutical science.

Another study further elucidates how the traditional borders separating the two sectors have blurred over the years because both sectors are “challenged to show returns on their investments.”\(^{14}\) This study also emphasizes that over the last few decades drug discovery has evolved into a system that is a “complex chain of interrelated events and it involves an incremental learning process that takes place over time.”\(^{15}\)

The primary aim of the current paper is to follow up the 2008 analysis of 35 important drugs by Zycher, DiMasi & Milne. We focus here on a recently identified cohort of “the most transformative drugs of the past 25 years” as determined by a survey of medical practitioners conducted by two physician-scientists from Harvard Medical School in an article published in mid-2013.\(^ {16}\) By examining the publicly available scientific literature, the private collection of the Tufts University research libraries, as well as CSDD’s leased and proprietary databases, we ascertained the relative contributions of the public and private sectors to the basic research, discovery, development, and production for 19 individual drugs, 6 drug classes and 1 drug combination identified by Kesselheim and Avorn. The following section briefly summarizes the history of how these transformative medicines reached the marketplace by means of journeys that were often expansive in scope (countries and institutions) and extensive in time (usually decades), but nearly always with one commonality – their paths crisscrossed between both the public and private sectors.

**II. Methods & Results**

As discussed earlier, the current paper is a follow-up of a 2008 analysis, which tracked the same theme, but differed somewhat in approach in terms of the study cohort selection and methodology. We will briefly summarize them as they relate to the current study. The cohort in Zycher et al. was selected by merging lists from the literature of important drugs both from the perspective of impact on medical practice as well as utilization (i.e., numbers of prescriptions). Appropriate cohort selection is especially critical for informative work on this subject matter. Certain characteristics are desirable: medicines that serve an important role in healthcare; retain their socio-medico importance currently or have done so until fairly recently; were developed over a period of time (i.e., not all in a quick burst of public health urgency and extraordinary resource allocation such as with AIDS drugs in the decade from the mid-1980s to the mid-1990s); are broad-based in terms of therapeutic areas; and finally, were selected on the basis of fulfilling these criteria without any pre-selection bias. For these reasons, the authors chose to examine a cohort of drugs from a recently published work – *The Most Transformational Drugs of the Last 25 Years* (Kesselheim & Avorn, 2013) – that, generally speaking, demonstrated these characteristics. Since a detailed discussion of

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\(^{15}\) Ibid

the selected cohort is outside the scope and intent of this paper, the readers can judge for themselves by perusing the paper, which was published in a major scientific journal by authors who have often been critical of the pharmaceutical industry. There are several advantages to this cohort of drugs compared to the one analyzed in 2008: less risk of selection bias; more narrow focus mostly on individual drugs over a more concentrated period of R&D; and, the drugs have been judged to be important by a survey of nearly 200 expert physicians across 15 specialties from 30 leading academic medical centers.

In terms of the methodology, we were informed by our prior studies but relied on a wider variety of resources that had become available to us over time: case files on individual drugs previously studied by Tufts CSDD; two previous analyses of impact drugs conducted by Tufts CSDD; data extracted from Tufts CSDD proprietary databases and commercial databases to which CSDD leases access; drugs@fda; the Merck index; Google searches; as well as background literature from professional journals, trade press, textbooks and historical reviews of drug origins. The initial review was guided by certain criteria and categorical determinations provided by the senior authors and informed by prior CSDD research. It consisted of extracting a plethora of information on contributions to various milestones in the R&D history of the targeted drugs: disease process, drug target, mechanism of action, drug concept, isolation and purification, synthesis and early testing, patenting, lead optimization, pre-clinical studies, formulation and manufacturing protocols, clinical development, approval and launch. Upon second review, the data was condensed into a manageable quantum relegated to four categories that appear in Table 1 (basic research, discovery, chemistry/manufacturing & formulation/controls [CMC], and development). Gaps in the available data were identified, and a preliminary assessment of which sector provided the dominant contribution for each R&D phase of each drug was undertaken. Sometimes this could not be determined because of data gaps or the complexity of assigning a dominant contributor to highly inter-related work. Research team members who conducted the first review of a particular medicine switched with other team members for second reviews, with a final review by the senior researchers, so that all drugs were “touched” by more than one researcher.
Table 1: Major Contribution (e.g., target identification/validation, patents, proof-of-concept, FDA approval) to R&D of Study Drugs with Breakdown by Sector and Phase

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Basic Research</th>
<th>Discovery</th>
<th>CMC</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alglucerase</td>
<td>Private</td>
<td>Public</td>
<td>Private</td>
<td>Public</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Public/Private</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Epoetin Alfa</td>
<td>Public</td>
<td>Public/Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Public</td>
<td>Public/Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>Public</td>
<td>Public</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Public/Private</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Metformin</td>
<td>Public</td>
<td>Public</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Nitisinone</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
<td>Public/Private</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Public</td>
<td>Private</td>
<td>Private</td>
<td>Public/Private</td>
</tr>
<tr>
<td>Propofol</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
<td>Public/Private</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Public/Private</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Public</td>
<td>Private</td>
<td>Private</td>
<td>Public/Private</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Public</td>
<td>Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>Public</td>
<td>Private</td>
<td>Public/Private</td>
<td>Private</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Public</td>
<td>Public/Private</td>
<td>Public/Private</td>
<td>Private</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classes</th>
<th>Basic Research</th>
<th>Discovery</th>
<th>CMC</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Public</td>
<td>Public/Private</td>
<td>Public/Private</td>
<td>Private</td>
</tr>
<tr>
<td>Anti-VEGF agents</td>
<td>Public</td>
<td>Private</td>
<td>Public/Private</td>
<td>Private</td>
</tr>
<tr>
<td>Biophosphonates</td>
<td>Public</td>
<td>Public</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>HIV Protease Inhibitors</td>
<td>Public/Private</td>
<td>Public/Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>Interfons beta-1b, 1a</td>
<td>Public</td>
<td>Public/Private</td>
<td>Private</td>
<td>Private</td>
</tr>
<tr>
<td>TNF blockers</td>
<td>Public/Private</td>
<td>Public/Private</td>
<td>Public/Private</td>
<td>Public/Private</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Combination</th>
<th>Basic Research</th>
<th>Discovery</th>
<th>CMC</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined fluticasone and salmeterol</td>
<td>Public</td>
<td>Private</td>
<td>Public/Private</td>
<td>Private</td>
</tr>
</tbody>
</table>

The results as seen in Table 1 basically represent a graphic retelling of the story line from the summary case histories (see Appendix) – very few drugs went from theory to therapy without work being done on them by both the private and public sectors. In fact, only 4 individual drugs appear to have had been almost completely researched and developed by one sector – in the current study, it was the private sector (although not necessarily without any contribution by the public sector at all (epoprostenol) and sometimes because of a significant element of serendipity (sildenafil).
On the other hand, as seen in Table 2, all of the four phases of R&D are dominated by one or the other sector. For example, 54% of basic science milestones were achieved predominantly by the public sector, and 27% by the private sector. For discovery milestones, it was 15% by the public sector, and 58% by the private sector. The private sector was again dominant in achieving the major milestones for both the CMC phase and development phase, in 81% and 73% of the drugs reviewed, respectively. From 19 to 27% of the case histories in all four phases, dominance of one sector versus the other could not be determined.

Table 2: Percent Contribution in 4 Phases of R&D by Public and Private Sectors

<table>
<thead>
<tr>
<th>Basic</th>
<th>Discovery</th>
<th>CMC</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>54% Public</td>
<td>58% Private</td>
<td>81% Private</td>
<td>73% Private</td>
</tr>
</tbody>
</table>

Among the many important steps that occur during the translational phase (represented graphically in Table 2) is target validation – one of the greatest challenges in drug discovery. Basic scientific research carried out by academia, government researchers and industry explores the complex biology and causes of diseases and in doing so may identify a disease protein, a receptor or an enzyme (drug targets), that are implicated in the disease. In private sector research, efforts are largely focused on developing new medicines that act upon these receptors or enzymes in order to create improvements in the disease condition. However, not all discoveries of potential targets are
directly applicable to the development of new medicines. In fact, the vast majority of potential targets discovered in basic science research must still be re-validated as the first step in the discovery research process. Thus the meaning of the term ‘translational’ phase becomes clear – the transfer of knowledge of underlying disease biology into a research hypothesis that is further explored and eventually confirmed by 10 to 15 years of discovery research, preclinical research, and clinical development that hopefully leads to an important new medicine.\textsuperscript{17}

As shown in Table 3, no particular therapeutic area dominates the cohort and a dozen or so of the major therapeutic areas are represented among the individual drugs, indicating that this cohort likely broadly reflects trends in drug development as a whole. Nearly 70\% of these drugs are available as generics in the US, and one is available as an OTC product as well, while another is available in Japan as a biosimilar. As valuable as these drugs are to medical practice, they are also making contributions to the value of the healthcare dollars spent in medical systems worldwide. In fact, nearly 40\% of the drugs are listed on the World Health Organization Model List of Essential Drugs, which comprises the list of some 300 drugs considered essential for any particular country to be able to provide its population because they are therapeutically important, affordable and generally in ready supply in appropriate formulations. In addition, nearly 40\% of the drugs have orphan indications, thereby providing therapy for rare disease populations, likely for unmet medical needs for which there were few if any treatment options. Almost all of these drugs have been launched on a worldwide basis and are still actively in development for additional indications or formulation improvements.

Although Tables 1-3 suggest the complexity and diversity of the research origins of our drug cohort, there are other spheres in which these defining characteristics are also evident – length of time and breadth of geography. While the headquarters of the sponsoring companies are located in just five countries, research took place in nearly two dozen countries. On the whole, R&D occurred from the 1950s through the 1980s, with approvals for initial indications occurring for the most part during the late 1980s through the early 2000s. On average, the time from initial discovery efforts to approval took 25 years. The basic research often had been going on for a decade or two prior to discovery, while further development on new indications or formulations continue to this day on many of these transformative drugs.

Our compilation of case summaries on the drugs and drug combination/classes in our study revealed seven underlying themes that characterize each of their histories (and some cases evidence more than one theme): drug rescue; technical fix; screening programs; serendipity; spin-offs; drug champions; and sector-sharing.

**Drug rescue** – A salient aspect of the story of clozapine is that of a drug abandoned for a time due to safety risks but rescued to address an unmet medical need owing to advocacy and incentive programs provided by the public sector coupled with the perseverance, expertise, and resources of the private sector. Metformin highlights another example of the private sector continuing to pursue a

\textsuperscript{17} A Research & Development Ecosystem for the 21st Century, Pfizer Presentation, May 2, 2014
Table 3: Therapeutic Area (TA), Generic, WHO Essential Drugs List (EDL, April 2013), and Orphan Approval

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>TA</th>
<th>Generic</th>
<th>WHO EDL</th>
<th>Orphan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alglucerase</td>
<td>Metabolic</td>
<td>N</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Mental Health</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Epoetin Alfa</td>
<td>Blood Disorder</td>
<td>N</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Inflammation</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Mental Health</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Oncology</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latanoprost</td>
<td>Ophthalmology</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<td>Lovastatin</td>
<td>CV</td>
<td>Y</td>
<td></td>
<td>N</td>
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<td>Metformin</td>
<td>Endocrine</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
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<td>Nitisinone</td>
<td>Metabolic</td>
<td>N</td>
<td></td>
<td>Y</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>GI</td>
<td>Y/OTC</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Nerve Disorder</td>
<td>N</td>
<td></td>
<td>N</td>
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<td>Propofol</td>
<td>Anesthesia</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<td>Remifentanil</td>
<td>Anesthesia</td>
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<td></td>
<td>N</td>
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<td>Rituximab</td>
<td>Oncology</td>
<td>N</td>
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<td>N</td>
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<tr>
<td>Sildenafil</td>
<td>Uro/Gen</td>
<td>Y</td>
<td></td>
<td>N</td>
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<td>Sumatriptan</td>
<td>Pain</td>
<td>Y</td>
<td></td>
<td>N</td>
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<td>Tamsulosin</td>
<td>Uro/Gen</td>
<td>Y</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>HIV/AIDS</td>
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<td>Y</td>
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**Classes**

<table>
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<th>Class</th>
<th>TA</th>
<th>Generic</th>
<th>WHO EDL</th>
<th>Orphan</th>
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</thead>
<tbody>
<tr>
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<td>CV</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<td>Oncology</td>
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<td></td>
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<td>Musculo-skeletal</td>
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<td>HIV/AIDS</td>
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<td>Y</td>
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<td>Immune</td>
<td>Y- ex US</td>
<td></td>
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<tr>
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<tr>
<td>TNF blockers</td>
<td>Inflammation</td>
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**Combinations**

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<td>Respiratory</td>
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drug with some challenges at the prompting of talented and visionary researchers in the broader medical research community. In similar vein, an example of perseverence when confronted with risk, albeit acceptable ones (due to its potential for meeting an unmet medical need) was shown on the part of the private sector by continuing to address medical concerns over a number of years until a seminal clinical study put the issue to rest for lovastatin.

**Technical fix** – Although not as common or compelling a theme for this cohort of drugs as with the 2008 cohort, the history of **epoetin alfa** shows how the decades long advance of basic research and early discovery towards clinical application was stymied until the technical problem of producing it in sufficient quantity was worked out by the private sector. Similarly, while **interferon** too owed its discovery and development to a significant overlap between the two sectors, working out the challenges of commercial production was the province of the private sector.

**Screening programs** – A common theme that emerges from our reviews is that drug companies during this time period had ongoing screening programs that were proactively on the lookout by various means for candidate compounds to address unmet medical needs with commercial potential. This is how **epoprostenol** came about, and **omeprazole** as well. The latter, however, is a somewhat atypical story of primarily being engendered from the efforts of one sector, but exemplifies the productivity of pharma company screening programs of candidate compounds for common conditions that nonetheless qualify as unmet medical needs. **Propofol, reminfentanil,** and **tamsulosin** continue the theme of drug companies pursuing screening programs for candidate drugs to address apparent areas of unmet need, but in their case providing the resources in terms of funding and/or investigative compounds to clinical researchers at academic medical centers. While much of the basic research and discovery work was done in the public sector, GSK’s screening program certainly accelerated the pace of development of **zidovudine**. The development of **ACE inhibitors** and **sumatriptan** appear to be examples of company screening programs picking up some promising leads from the basic research available in the public sector on population-wide health problems and facilitating public sector research until a candidate drug emerged.

**Serendipity** – Somewhat in contrast to the role of screening programs in which companies are actively on the lookout for compounds to address identified needs, the ubiquitous scientific interloper of serendipity makes an appearance in a couple of our case histories. The fact that **nitisinone** was originally developed as an herbicide shows how serendipity can play a role in the origin of drugs. However, as the saying goes, luck favors the prepared mind. The discovery of **sildenafil** was the result of both a good data monitoring program and an astute researcher noting an unexpected side effect that resulted in the melding of a commercial opportunity with an unmet medical need.

**Spin-offs** – Crucial to the R&D efforts of **alglucerase** and representative of the interdependence of public and private sectors was Henry E. Blair of the New England Enzyme Center, based at Tufts University, who later co-founded a private company to focus on orphan drugs that became Genzyme Corporation, now one of the largest biotech companies in the world, which in turn
played no small part in precipitating the biotech revolution. The development of onabotulinum-toxin A is another example of research started in the public sector by the original inventors, who transformed their efforts into private sector enterprises, such as Miotech and Oculinum (later acquired by Allergan).

**Drug champions** – Fluoxetine exemplifies that the decades-long journey of a drug from lab bench to market shelf requires many champions along the way both in the private and public sector, who often keep a program going by maintaining progress in one sector when it encounters roadblocks in another. While the initial discoveries relating to the causes of CML were publicly funded, the actual development of imatinib was the result of a fruitful collaboration between the private and public sectors, and another instance of drug champions moving between sectors to keep research from dying on the vine.

**Sector-sharing** – The last and most prevalent of our themes is sector-sharing, or the tendency of drug histories to reveal that the primary role for moving a particular medical innovation forward often involves bi-directional feedback between the sectors with “sharing” occurring along paths that were both planned and unplanned. For example, while research performed in the public sector (at Columbia University) was absolutely critical for the development of latanoprost, a collaboration with the private sector allowed it to be developed into the blockbuster drug it became. This was the case with rituximab as well, which was primarily worked on in the public sector through the upstream R&D phases of basic research and discovery, and only later collaboratively in downstream studies with the private sector. This was the mirror image of the way the combination drug of fluticasone and salmeterol came about, with upstream studies demonstrating that they were effective when used in combination being largely performed or funded by the private sector with Glaxo playing the dominant role. For downstream development, Glaxo worked collaboratively by funding clinical trials at various academic medical centers while it addressed drug delivery. Somewhat departing from this scheme were the Anti-VEGF agents with publicly-funded studies establishing the concept that angiogenesis is a critical aspect of tumor growth and a potential anti-cancer target, but private research early on led to the discovery of both the pro-angiogenic factor and a method to target its activity in a manner suitable for the clinic. The bisphosphonates were similar in that the concept that they could be used as a therapy for bone disorders began in publicly-funded laboratories in Switzerland, but collaborations with industry were absolutely critical for the development of the drugs that were eventually approved. HIV protease inhibitors were the mirror image of bisphosphonates, being developed primarily by the private sector, but dependent upon initial discoveries made by a combination of publicly- and privately-funded research. Lastly, both the identification of TNF-alpha as a target for autoimmune disease and the subsequent development of therapies that targeted it were the result of a number of collaborations between the private and public sectors.
III. Policy Implications

The results of our analysis of case histories for the most transformative drugs over the last 25 years confirms just how critical the private sector is to the time and resource consuming process of drug development. But some remain skeptical of the role of the private sector in this important enterprise, and assert that it could and should be exclusively within control (at least financially) of the government. This begs the question. How Much Government Funding Would be Needed to Replace Industry New Drug R&D?

As an alternative to the current system of private sector biopharmaceutical R&D supported by intellectual property protection, some have advocated for replacing industry conducted and funded biopharmaceutical R&D with government funding the R&D process in full by either conducting the R&D itself or directly contracting for it. Legislation to that effect had been proposed in the United States Congress. Such a system would have to be supported by additional taxes. There are a number of serious drawbacks to such an approach. These include adverse selection in the disease categories emphasized if politics intrude on decision-making and inefficiencies resulting from the difficulty of administrators to judge the effectiveness of R&D activities and to align R&D objectives with consumer demand. The nature of the current government grants process in life sciences also suggests that discovery and development would proceed less efficiently and more conservatively than it does currently in the private sector.

Discussions of the costs and benefits of replacing industry R&D with direct government control can be better informed with data. Consequently, we made an effort to conservatively assess what the additional cost to government and taxpayers would be if such a radical policy change were adopted. To have an analysis that is consistent with the period covered by the particular innovative compounds that we study in detail in this report, we first restricted attention to new drugs approved from 1987 to 2002. This period for approvals also dovetails nicely with a published study of R&D costs per approved new compound incurred by industry. Given the number of new drug approvals over this period, we can then estimate the aggregate industrial expenditures incurred to obtain those approvals (inclusive of the costs of research failures) and compare the ongoing costs of sustaining that level of output with the amount spent on life sciences research by the U.S. federal agency that is overwhelmingly responsible for funding that research (the National Institutes of Health [NIH]). We also then apply this technique using a more recent R&D cost analysis and a more recent approval period (2003 to 2011).

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The DiMasi et al. (2003) study of industry R&D costs included estimates of the time costs of new drug development, along with estimates of the cash outlays (out-of-pocket costs). Since cash outlays, in theory, can be capitalized at different rates depending on whether industry or government is conducting the R&D, we restrict our attention to cash outlays. For a list of approvals, we utilized some of the data for a study conducted by Food and Drug Administration (FDA) researchers that grouped approvals of therapeutic new molecular entities (NMEs) into innovation categories. The compounds included in the study were new drugs and biologics evaluated by the FDA’s Center for Drug Evaluation and Research (CDER) from 1987 to 2011, excluding diagnostics, drugs approved under the 505b(2) regulatory pathway, and compounds used only for military personnel.

The Lanthier et al. (2013) study grouped the new drug and biologic approvals into three innovation categories. The three categories are first-in-class, advance-in-class, and addition-to-class. First-in-class drugs represent pharmacological innovation, as drugs with new mechanisms of action, or other novel pharmacologic properties, are brought to market for the first time. Compounds in the advance-in-class category were not first-in-class approvals, but had received a priority review rating from the FDA (potential significant gain over existing therapy). The addition-to-class category includes all other approvals. The annual averages for the number of approvals in each of these categories for our initial period of analysis (1987-2002) are shown in Figure 2.

**Figure 2. Therapeutic New Molecular Entity Approvals (1987-2002) by Innovation Category**

The combination of the first-in-class and advance-in-class categories accounts for nearly half of all the new drug approvals. For the purposes of our analysis, we combine first-in-class and advance-in-class compounds into what we shall call a “most innovative” category. We developed aggregate cost

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estimates from the published literature for both the most innovative category and for all approvals from 1987 to 2002.

DiMasi et al. (2003) provides average cost estimates in year 2000 dollars for out-of-pocket costs for a period that corresponds closely with the approval period we are using. Thus, we use the figures in that study adjusted for inflation to year 2013 dollars by applying the same price index used for the study (GDP Implicit Price Deflator). Doing so yields an out-of-pocket cost per approved compound, inclusive of the cost of failures, of $526 million. The clinical period out-of-pocket cost estimate across all compounds is $368 million, while the pre-human cost estimate is $158 million.

The DiMasi et al. (2003) study results allow for some differentiation based on the FDA review ratings of the approved products. The results for the period covered had average clinical period costs for approved drugs with a priority rating that were 33.5% higher than for drugs with a standard rating. We will assume that the higher relative costs for priority drugs carries over to failures. Then, utilizing the distribution of the drugs approved from 1987 to 2002 by FDA therapeutic rating (43.3% priority and 56.7% standard), we can decompose the $368 million clinical period cost per approved drug over all drugs into $429 million for priority drugs and $321 million for drugs with standard ratings. Absent evidence about differentiation on the pre-human side, we assume that the overall average applies to both priority and standard drugs. This then yields estimates of total out-of-pocket costs per approved compound of $587 million for drugs with priority ratings and $479 for drugs with standard ratings.

Given the above cost estimates for priority and standard drugs, and the numbers of approvals from 1987 to 2002 in the most innovative category and for all drugs, we calculated the cost of developing the most innovative drugs approved from 1987 to 2002 in aggregate to be $128 billion, and the cost of developing all of the drugs approved from 1987 to 2002 to be $234 billion. When considered on an average annual basis, these results amount to $8.0 billion per year for priority approvals and $14.7 billion per year for all new therapeutic approvals.

R&D efforts typically continue after original new drug approval to test new dosage strengths and regimens, new formulations, new indications, and to meet regulatory post-marketing commitments. Thus, we can define lifecycle R&D costs as the sum of R&D expenditures prior to and post original approval. DiMasi et al. (2003) found that post-approval R&D cost per approved compound to be 34.8% that of pre-approval R&D cost. This implies a post-approval R&D cost per approved compound of $183 million. We have no evidentiary basis to distinguish between priority and standard drugs for post-approval costs, although it may well be the case that more post-approval R&D is done for drugs with priority ratings. However, we conservatively assume that post-approval cost per approved compound is the same whether the drug received a priority or a standard rating. Thus, the implied lifecycle cost per approved compound is $770 million for drugs with priority ratings and $662 million for drugs with standard ratings. These figures translate to lifecycle R&D costs of

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24 Ten of the 446 approvals were biologics approved early in the period that did not receive FDA therapeutic significance ratings. We made judgment calls and assigned ratings for these compounds based on the Lanthier et al. (2013) innovation categorization and other considerations.
$169 billion for the most innovative compounds and $316 billion for all compounds. On an average lifecycle R&D cost per year basis, we then have $10.6 billion for most innovative compounds and $19.8 billion for all compounds.

We can now compare industry costs to total NIH budget expenditures. We ask what would be the cost to government of assuming industry R&D expenditures so as to maintain a steady-state level of approvals consistent with what we have seen for the 1987 to 2002 period in comparison to NIH budget levels. First, we observe what total appropriations have been for the NIH by fiscal year from 1976 to 2013. Figure 3 shows those values in constant (year 2013) dollars.²⁵

![Figure 3. Inflation-Adjusted NIH Budget (2013 $), 1976-2013](http://www.nih.gov/about/almanac/appropriations/part2.htm; author calculations using the GDP Implicit Price Deflator)

The initial year is significant for us as DiMasi et al. (2003) found a representative time profile for new drug development of approximately 12 years. Thus, initial work on 1987 approvals would have begun, on average, in 1976. The average annual total NIH budget between 1976 and 2002 was $13.4 billion.

We consider the annual costs noted above as the amounts needed to maintain a steady-state of approvals and compare them to the average annual NIH budget over the period analyzed. Figure 4 shows how much more taxpayers would have to pay to have government replace industry as a funder of new drug development in relation to what it already pays to fund the NIH.

²⁵ For consistency, and taking the perspective that dollars spent by industry and taxpayers have alternative uses, we applied the same general economy-wide price index as was used for the industry R&D cost data. The Biomedical Research and Development Price Index (BRDPI) was developed using NIH inputs to reflect how much the NIH budget must change to maintain purchasing power for its activities. It generally shows more price inflation than does the GDP Implicit Price Deflator. Applying the BRDPI to the NIH budget data would show the same general pattern, but a lower rate of increase over time (for the portion of the period where real expenditures were rising) than is suggested by Figure 2.
The estimates suggest that the NIH budget would have to nearly double to maintain just the flow of the most innovative drug approvals, and would have to increase nearly two-and-half times to maintain the development of all new drugs. Note, though, that these are likely very conservative estimates of how much extra it would cost government to replace what industry does. NIH research-funded endeavors are generally not set up to meet the rigorous demands of regulatory approval authorities. This relative inexperience would likely result in the government spending significantly more on developing new drugs than does the industry (at least for a significant period of time). Furthermore, as can be seen from Figure 3, in real terms subsequent to our period of analysis NIH funding has been relatively flat, and even declining in some years. In contrast, drug development costs have increased significantly in real terms for decades, and, given data on increasing clinical trial complexity and declining clinical approval success rates for recent years, it is likely that an analysis that covered a more recent period than we have analyzed would show substantially higher industry R&D expenditures in relation to government-supported life sciences research. 

We turn now to an analysis that utilizes more recent development cost estimates and data on more recent approvals. The Lanthier et al. (2013) data run to 2011 approvals. Thus, we focus on 2003 to 2011 U.S. new drug approvals. A new study of private sector R&D costs (http://csdd.tufts.edu/files/

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uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf) corresponds approximately to this period. In 2013 dollars, the out-of-pocket cost per approved new compound is $1.395 billion. Of that amount, $965 million is associated with the clinical period while the pre-human cost estimate is $430 million.

For the new analysis, standard rated drugs had higher average costs, and the share of approvals over the 2003 to 2011 period that received priority ratings was somewhat higher than for the prior period (48.2% priority and 51.7% standard). Applying the same methodological approach used for the 1987 to 2002 approvals, we decompose the $965 million clinical period cost per approved compound into $787 million for priority drugs and $1.132 billion for standard drugs. Under the same assumptions applied above, we apply estimates of total cost per approved compound of $1.217 billion for drugs with priority ratings and $1.562 billion for drugs with standard ratings. Given these estimates, we calculated that the cost of developing the most innovative drugs approved from 2003 to 2011 to be $156 billion, and the cost of developing all drugs to be $278 billion. On an average annual basis, the results are $17.3 billion for priority approvals and $30.9 billion per year for all new therapeutic approvals.

The new R&D cost study also includes estimates of post-approval R&D. The post-approval out-of-pocket cost per approved compound is $466 million. Using the same assumptions noted above regarding the allocation of post-approval costs for priority and standard approvals, we estimate the lifecycle R&D cost per approved compound to be $1.683 billion for drugs with priority ratings and $2.028 billion for drugs with standard ratings. These values translate to lifecycle R&D costs of $212 billion for the most innovative compounds and $370 billion for all compounds. On an average annual basis, this implies that lifecycle R&D cost is $23.6 billion for the most innovative compounds and $41.2 billion for all compounds.

Figure 5. Additions to the NIH Budget Needed to Replace Industry R&D Funding of Therapeutic New Molecular Entities (2003-2011 approvals)

Sources: Lanthier et al., Health Aff, 2013;32(8):1433-1439; author calculations
To compare these new figures to NIH budget numbers, we have to use more recent years than we did above. For the new study initial development work began, on average, approximately 11 years prior to approval. Thus, for the new analysis, we use NIH budget numbers from 1993 to 2011. The average annual NIH budget over that period was $25.9 billion.

Figure 5 shows the additions in percentage terms to the amounts spent on the NIH needed to maintain the same flow of drugs that were approved from 2003 to 2011. Given rising R&D costs and declines in the rate of increase in NIH budgets in real terms, we have higher relative costs for both most innovative drugs and for all drugs, and for both pre-approval and lifecycle R&D than we observed for the 1987 to 2002 approvals. Note that the NIH budget had still been increasing at a significant rate over the first half of the period used in this analysis. The relatively flat NIH budget levels over the latter half of the period suggest that an analysis of more recent and future approvals will show more substantial increases in the relative cost of private sector R&D.

IV. Conclusion

Far from being a bystander in the decades-long efforts that result in therapeutically important drugs until the point of marketing, industry’s scientific contributions go beyond drug development and include basic and applied science, discovery technologies, and manufacturing protocols. The fact that only a dozen and half drugs and a half dozen drug classes were chosen as being transformative over the last 25 years highlights just how important it is to maximize resources to ensure that every possible lead compound is pursued until its potential has been fully explored. With available funding from the public sector decreasing while medical needs and scientific complexity increase, private sector collaboration with academia and government have become increasingly key in furthering medical advancement. However, no laboratory discovery, no matter how profound, can help a single patient until it can be tested and evaluated in people. The ability to translate knowledge about biological processes into a medicine or vaccine with the appropriate drug-like properties and a clinically meaningful benefit is the unique domain of the biopharmaceutical industry. Even Médecins Sans Frontières (MSF), an independent medical humanitarian organization on the front lines of public health emergencies like the Ebola outbreak in West Africa, who are sometimes critical of Big Pharma, acknowledges the reality of the respective roles of the two sectors: “[w]hile supporting basic and drug-lead discovery research, the public sector has rarely developed its own drug development expertise and capacity…[t]he expertise, infrastructure and management capacity for moving these discoveries through the drug development process is concentrated in the private sector.” 28 Therefore, without private investment in drug development there would be no return on tax payer investment in basic science.

28 Source: Medecins Sans Frontieres, Fatal Imbalance, 18-19.
Appendix A.

Summary Case Histories

Drugs & Biologicals

Alglucerase (Ceredase) is a modified form of human β-glucocerebrosidase enzyme which treats a deficiency of the enzyme that causes Type 1 Gaucher’s disease. Alglucerase was an orphan product (defined in the US as treating conditions with a prevalence of 200,000 or less) and the first drug approved as an enzyme replacement therapy. Genzyme first pursued development of alglucerase but the cost of production had always been a challenge. Alglucerase is a placenta-derived product and required massive investment for the harvesting and transport of placentae, industrial scale purification of the enzyme, and carbohydrate remodeling. When it came time for early pivotal trials, it was made possible by a combination of funding from the company, the NIH, and the National Gaucher Foundation. Ceredase was first approved by the FDA in 1991 but then later withdrawn from the market due to the approval of similar drugs; these drugs were made with recombinant DNA technology, removed concerns about diseases being transmitted from the tissue used in harvesting, and were less expensive to manufacture. In 1997, completion of a large scale manufacturing facility allowed the majority of patients to transition from alglucerase to imiglucerase (Cerezyme). Unlike algucerase which was supplied as a protein solution containing a mild solubilizing agent and was partially contaminated by proteins such as human chorionic gonadotropin, imiglucerase is supplied as a pure lyophilized product and is reconstituted in water for clinical use. Among the many hurdles needed to be cleared in order for Ceredase to arrive at its point where it is today, the most important was to produce enough of the active enzyme in a purified form early on from human sources. Crucial to these R&D efforts and representative of the interdependence of public and private sectors was Henry E. Blair of the New England Enzyme Center, based at Tufts University, who later co-founded Genzyme Corporation, which in turn played no small part in precipitating the biotech revolution.29,30,31

Clozapine is an atypical antipsychotic medication used in the treatment of schizophrenia. The discovery was made possible in the 1950s by early clinical trials in Canadian hospitals which then went on to prompt a large number of research programs by pharmaceutical companies that focused on compounds for anti-psychosis. Clozapine was the first of the atypical antipsychotics that resulted from these company screening programs; it was first introduced in Europe in 1971 but voluntarily withdrawn by the manufacturer in 1975 when patients taking the drug were shown to be at a high risk for agranulocytosis (precipitous drop in WBCs) along with some deaths. As a result, it was then dropped from development in US. In the 1980s, Sandoz (later to merge with Novartis) chose

29 Review of early history, NIH role, etc. at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3340106/pdf/dddt-6-081.pdf
30 Review of switchover to imiglucerase, scale-up problems, etc. at http://www.sciencedirect.com/science/article/pii/S1096719206002976
31 Deegan PB, Cox TM. Imiglucerase in the treatment of Gaucher disease: a history and perspective. Drug design, development and therapy. 2012; 6: 81-106
to re-evaluate clozapine as medical understanding of agranulocytosis increased and studies, in particular by John Kane at Hillside Hospital in Glen Oaks, NY, demonstrated that it was effective in mitigating treatment-resistant schizophrenia. Sandoz’s decision to persevere with clozapine was advocated by the overall psychiatry profession, the NIH, and the FDA. The 1984 Hatch-Waxman Act, which provided 5 years of market exclusivity for NCEs, also helped Sandoz move forward due to the fact that the drug’s patent had run its course. Pharma continued providing the drug to academic medical centers to further work on its clinical benefits while the company worked out a risk management program. Sandoz resubmitted the NDA in 1987, received FDA approval in 1989, and clozapine entered the market in 1990. Clozapine is one of the most effective anti-psychotic treatment choices and demonstrates the least likelihood of serious side-effects. It is currently on the World Health Organization’s Model List of Essential Drugs (WHO EML) with expanded indications for treatment-resistant schizophrenia. A salient aspect of the story of clozapine is that of a drug abandoned for a time due to safety risks but resurrected to address an unmet medical need due to advocacy and incentive programs provided by the public sector coupled with the perseverance, expertise, and resources of the private sector.32,33,34,35

Epoetin alfa is a human erythropoietin produced in cell culture using recombinant DNA technology that mimics the naturally occurring hormone that stimulates erythropoiesis. In the early 1900s, university researchers Carnot and Deflandre attributed an increase in red blood cells in rabbits to a hemotropic factor called hemopoietin. Further studies by Reisman and Erslev (Thomas Jefferson Medical College) demonstrated that an unknown substance was able to stimulate red blood cell production and increase hematocrit. Eugene Goldwasser (1976), a researcher at the University of Chicago, discovered that the substance was the hormone erythropoietin. Subsequent NIH-funded research at Columbia University invented and patented a technique for synthesizing the protein and patented this. Production of a recombinant version was reported in Feb. 1985 by a team of researchers from the biotechnology company Genetics Institute, Kumamoto University, and Wright State University, as well as with support from Chugai Pharmaceuticals of Japan. Although EPO was capable of being isolated from human urine, researchers were unable to produce it in significant qualities for medical use. Amgen obtained a license for the technique and was able to achieve large-scale commercial production of the erythropoietin molecule. From 1987 to 1989, reports were published on the results of trials involving small numbers of patients that were supported by Amgen, Ortho Pharmaceutical, and the NIH. It was approved in Japan and Europe, and as an orphan drug in the US, and marketed for the treatment of anemia due to chronic kidney disease, zidovudine treatment in HIV-infected patients, myelodysplasia from the treatment of cancer (chemotherapy and radiation), but primarily for the treatment of anemia associated with end-stage renal failure. The history of epoetin alfa shows how the decade’s long advance of basic research and early discovery

33 Naheed & Green (2001). Focus on Clozapine. *Current Medical Research and Opinion* 17(3): 223-229
35 Sneader W. *Drug Discovery: A History*. Wiley; 2005
towards clinical application was stymied until the technical problem of producing it in sufficient quantity was worked out by the private sector.36,37,38,39,40, 41

**Epoprostenol**, originally referred to as prostacyclin (or PGI2), is a prostaglandin that inhibits platelet activation and acts as a vasodilator. Prostaglandins (PGs) are made naturally by almost all tissues and can be synthesized from polyunsaturated fatty acids. They were discovered in 1933 in Sweden by von Euler (a physiologist and a pharmacologist) during his postdoctoral work. In the 1960s, a U.K. research team, headed by Sir John Vane, began to explore the role of prostaglandins in anaphylaxis and respiratory diseases. Working with a team from the Royal College of Surgeons, Vane discovered that aspirin and other oral anti-inflammatory drugs work by inhibiting the synthesis of prostaglandins. Vane and a team from the Wellcome Foundation identified a lipid mediator they called "PG-X," which inhibits platelet aggregation. PG-X, which later would become known as prostacyclin, was 30 times more potent than any other then-known anti-aggregatory agent. By 1976, Sir John and fellow researchers at Upjohn and Wellcome synthesized a molecule, which was given the name epoprostenol. But, as with native prostacyclin, the structure of the epoprostenol molecule proved to be unstable in solution and prone to rapid degradation. The research team synthesized nearly 1,000 analogues from which epoprostenol emerged. GSK got an orphan approval in the US in 1995 and then became available as a generic in 2008. Another theme that emerges from the story of this drug is that drug companies during this time period had ongoing screening programs that were proactively on the lookout by various means for candidate compounds to address unmet medical needs with commercial potential.42,43,44,45

**Fluoxetine** is used for the treatment of major depressive disorder and obsessive-compulsive disorder as well as a host of other mental conditions and disorders. Fluoxetine's primary mechanism of action is selective 5-HT (serotonin) uptake inhibition resulting in extracellular serotonin levels remaining elevated. Discovery of imipramine, as well as work by NIH, led to development of the class of drugs called tricyclic antidepressants, which were drugs that inhibited serotonin. In the late 1960s, Pharmacological Laboratories, AB Astra performed two of several studies that found that tricyclic antidepressants and cocaine result in the accumulation of 5-HT in the brain. In the 1970s, evidence of the role of serotonin in depression began to emerge and thus formed the idea that enhancing serotonin neurotransmission would be a way to mediate antidepressant response. In particular, a Johns Hopkins University study described the kinetics of serotonin accumulation in the rat brain that was useful for Lilly in their search for a specific inhibitor of reuptake. Brian Molloy

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39 Kresge et al *J Biol Chem*; 2011; 286(6) : e2-e3
40 See Reichert and Milne (2002)
41 See Zycher et al. (2008)
45 Vane JR. Pharmacological profile of prostacyclin. *American Journal of Cardiology.* 1995; 75: 3A-10A
of Eli Lilly screened candidates for inhibition of norepinephrine and 5-HT uptake. They found N-methyl-phenoxyphenylpropylamine to be potent in this regard so analogues were synthesized, resulting in discovery of fluoxetine by a project team at Lilly. Lilly performed several studies further characterizing fluoxetine and started early-phase trials, which in 1979 demonstrated that fluoxetine had an anti-depressive effect in humans. Lilly received FDA approval for Prozac in 1987 for the treatment of major depressive disorder in December 1987. The US patent expired in August 2001 and hence generic formulations are now available. It is on the World Health Organization’s Model List of Essential Medicines. Fluoxetine exemplifies that the decade’s long journey of a drug from lab bench to market shelf requires many champions along the way both in the private and public sector, who often keep a program going by maintaining progress in one sector when it encounters roadblocks in another.\textsuperscript{46-55}

Imatinib’s journey to the marketplace began in 1960 when Nowell and Hungerford at the University of Pennsylvania observed that many patients with chronic myelogenous leukemia (CML) have an abnormal, small chromosome. This was termed the Philadelphia chromosome, and was eventually found to occur in 95\% of CML patients. It was not until the 1980s that scientists began to develop a better understanding of the meaning of this chromosome for CML patients and found that this translocation caused the fusion of the ABL tyrosine kinase and the BCR genes, which in turn precipitated over-activation, with subsequent proliferation, resistance to cell death, and eventual malignancy. Two 1990 studies (published from MIT/Harvard Medical School and Tufts, respectively) demonstrated that CML could be induced in mice by BCR-ABL. Further research during the 1980s and 1990s suggested that BCR-ABL was a potential drug target for CML. In 1988, Nick Lydon from Novartis (then Ciba-Geigy) approached Brian Druker at the Oregon Health Sciences University to discuss the development of drugs that would target cancer-causing enzymes. Druker suggested focusing on inhibitors against BCR-ABL in order to treat CML, and collaboration between the two groups began. The first report of the drug that would eventually become imatinib was published in 1996, when the two groups demonstrated that this drug was effective in preventing the growth of BCR-ABL positive cells. Once Ciba-Geigy merged with Novartis, Druker convinced the company to

\textsuperscript{46} Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. \textit{European journal of pharmacology.} 1997; 340(2-3): 249-258

\textsuperscript{47} Ross SB, Renyi AL. Inhibition of the uptake of tritiated catecholamines by antidepressant and related agents. \textit{European journal of pharmacology.} 1967; 2(3): 181-186

\textsuperscript{48} Ross SB, Renyi AL. Inhibition of the uptake of tritiated 5-hydroxytryptamine in brain tissue. \textit{European journal of pharmacology.} 1969; 7(3): 270-277

\textsuperscript{49} Shaskan EG, Snyder SH. Kinetics of serotonin accumulation into slices from rat brain: relationship to catecholamine uptake. \textit{The Journal of pharmacology and experimental therapeutics.} 1970; 175(2): 404-418

\textsuperscript{50} Wong DT, Perry KW, Bymaster FP. The Discovery of Fluoxetine Hydrochloride (Prozac). \textit{Nat Rev Drug Discov.} 2005; 4(9): 764-774


\textsuperscript{52} Fuller RW, Perry KW, Molloy BB. Effect of an uptake inhibitor on serotonin metabolism in rat brain: studies with 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine (Lilly 110140). \textit{Life sciences.} 1974; 15(6): 1161-1171

\textsuperscript{53} See Sneader (2005)

\textsuperscript{54} See Reichert and Milne (2002)

\textsuperscript{55} See Zycher et al. (2008)
continue into Phase I trials with the drug. Trials were met with unprecedented success and imatinib was termed a “miracle drug” in the cancer field. It was approved in 2001 and marketed as Gleevec. While the initial discoveries relating to the cause of CML were publicly-funded, the development of imatinib was the result of a fruitful collaboration between the private and public sectors, and another instance of drug champions moving between sectors to keep research from dying on the vine.56,57,58,59,60,61,62,63,64,65

Latanoprost was the result of research performed at Columbia University in 1969 that provided one of the first indications that prostaglandins were involved in the regulation of intraocular pressure, a major risk factor for vision loss caused by glaucoma. This prompted a number of studies that focused on the role of prostaglandins in this process. Work from the University of London in 1971 was the first to demonstrate that prostaglandin E1 administration in rabbits caused initial hypertension followed by a reduction in intraocular pressure. Similar work from László Bito and his colleagues at Columbia in the late 1970s confirmed this. This led researchers to believe that prostaglandins may serve as possible therapy for the reduction of intraocular pressure. Bito’s group at Columbia eventually found that topical application of prostaglandin F2α (PGF2α) onto the cornea of both healthy monkeys and those with glaucoma caused a prolonged reduction in intraocular pressure. This was one of the first indications that PGF2α could serve as a therapy for glaucoma. Two separate groups in the late 1980s found that PGF2α reduced intraocular pressure by increasing uveoscleral outflow. Given that PGF2α itself was fairly hydrophilic and could not cross the cornea easily, Bito’s group searched for compounds similar to PGF2α that could more easily cross the cornea and act as a hypotensive therapy. In 1984, they found that PGF2α esters, which could easily cross the cornea, reduced intraocular pressure well. Bito then collaborated with Pharmacia (now Pfizer) in order to identify the PGF2α ester that was best suited for the treatment of intraocular pressure in humans. This eventually led to the development of latanoprost. Latanoprost was approved by the FDA in 1996 for the treatment of glaucoma and ocular hypertension and was marketed by Pharmacia as Xalatan. Ultimately, while research performed in the public sector (at

58 Pray Nature Education. 2009; 1(1):37
59 Rowley JD. Ph1-positive leukaemia, including chronic myelogenous leukaemia. *Clincs in haematology.* 1980; 9(1): 55-86
Columbia) was absolutely critical for the development of latanoprost, a collaboration with the private sector allowed for it to be developed into the blockbuster drug it became.66,67,68,70,71,72,73,74,75,76

**Lovastatin** is a member of the drug class of statins, used in combination with diet, weight-loss, and exercise for lowering cholesterol in those with hypercholesterolemia to reduce risk of cardiovascular disease. In the 1950s, the Framingham study led by Dawber established an increasingly firm correlation between high plasma cholesterol and CHD mortality. Enabling discoveries in cholesterol-lowering agents were reported and they were introduced into clinical use in 1950s and 1960s. At the same time in the 1950s and 1960s, Merck Research laboratories was working on the biosynthetic pathways, involving HMG-CoA reductase. In the 1970s, Japanese microbiologist Akira Endo discovered compactin (ML236B), a product with an inhibitory effect on HMG-CoA reductase (rate-limiting enzyme in the cholesterol biosynthetic pathway). At the end of the 1970s, Alberts, Chen and others at Merck Research Laboratories found a potent inhibitor of HMG-CoA reductase in a fermentation broth of Aspergillus terreus that came to be called Lovastatin. In the 1980s M. Hirama synthesized compactin and used one of the intermediates to follow a different path to get to lovastatin. The path to blockbusterdom was not an easy one, as Merck suspended clinical trials with Lovastatin in order to conduct additional animal safety studies in 1980 but resumed clinical trials in 1982. Observed tolerability continued to be excellent, and lovastatin was the first statin approved by the FDA in 1987. There were, however, further cholesterol controversies with a phase 1 study in 1984 and phase 2 in 1990-1994. However, a five-year clinical outcome trials with pravastatin and lovastatin all demonstrated reduction of coronary events with very few adverse effects in 1995-1998. Here is another example of perseverance on the part of industry when confronted with risk in light of the contribution of lovastatin to addressing unmet medical needs.77,78,79

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68 Camras CB, Bito LZ, Eakins KE. Reduction of intraocular pressure by prostaglandins applied topically to the eye of conscious rabbits. *Invest. Ophthamol.* 1977; 16: 1125-1134
72 Alm A, Nilsson SFE, Uveoscleral outflow—a review. *Experimental Eye Research 2009; 88; 760-768
75 See Bito (1983)
77 See Sneader (2005)
78 See Reichert and Milne (2002)
79 See Zycher et al. (2008)
Metformin is an oral antidiabetic drug in the biguanide class used in the treatment of type 2 diabetes. Metformin works by suppressing glucose production by the liver. While previous studies had shown that guanides may have anti-diabetic effects, in 1922 at Trinity College (Dublin, Ireland), what eventually became known as metformin (dimethyl biguanide) was first synthesized and described in the literature. Metformin was forgotten for the next two decades as research shifted to insulin and other antidiabetic drugs. Interest in metformin was rekindled in the late 1940s after several reports that it could reduce blood sugar levels in people. In the late 1950s, at Aron Laboratories in France the anti-diabetic effects of several biguanides were studied. Meanwhile, Jean Sterne, a physician at the Hopital de la Pitie in Paris, first conducted studies with Metformin on humans for diabetes. In 1956, he selected dimethyl biguanide (metformin) for clinical development and proposed the name Glucophage (glucose eater) for the drug and published his results in 1957. Metformin was marketed by Aron Laboratories, which was acquired by Lipha Pharmaceuticals (which in turn was then acquired by Merck in 1991). It was introduced to the United Kingdom in 1958 and in Canada in 1972. Due to side effects, it was not marketed in the US until its approval by FDA in 1995. Metformin is now believed to be the most widely prescribed antidiabetic drug in the world. It is available in generic formulations. Metformin is one of only two oral antidiabetics in the World Health Organization Model List of Essential Medicines (the other being glibenclamide). Metformin highlights another example of the private sector continuing to pursue a drug with some challenges at the prompting of talented and visionary researchers in the broader medical research community.80,81,82

Nitisinone is a drug used to slow the effects of hereditary tyrosinemia type 1, which is an orphan disease previously treated by liver transplantation. The compound is a synthetic reversible inhibitor of 4-hydroxyphenylpyruvate dioxygenase, which is the second enzyme involved in the catabolism of tyrosine. Early studies found that many herbicides inhibit this enzyme. The Environmental Health Center Laboratories in Farmington, CT performed toxicity experiments for nitisinone on rats and mice and found that corneal lesions may occur from repeated exposure. Zeneca then performed further toxicology experiments to better understand the effects on animals. It concluded that corneal lesions resulted from accumulation of tyrosine; otherwise, it was not acutely toxic. They collaborated with Professor Lindstedt at the University of Gothenburg, who then found that nitisinone is a potent inhibitor of liver 4-hydroxyphenylpyruvate dioxygenase. Once this discovery was made, Zeneca sought to determine how 4-hydroxyphenylpyruvate dioxygenase could be used as a drug in the clinic. Development continued under AstraZeneca (formed by the merger of Astra and Zeneca in April 1999), who later licensed it to Swedish Orphan for worldwide development and marketing. It is marketed under the brand name Orfadin, which received orphan drug status in 1995. The fact

80 See Sneader (2005)
82 See Zycher et al. (2008)
that nitisinone was originally developed as an herbicide shows that serendipity can play a role in drug discovery, but as the saying goes, luck favors the prepared mind.\textsuperscript{83,84,85,86}

**Omeprazole** is a proton pump inhibitor used in the treatment of gastro-esophageal reflux disease (GERD) and a number of related GI disorders. In the 1960s, the pharmaceutical company Astra began screening for drugs to inhibit acid secretion. Haessle (within Astra) started a gastrointestinal research division to find a product that inhibited gastric acid secretion for peptic ulcers. Meanwhile in 1968, George Sachs and colleagues at Smith Kline & French began work that discovered the proton pump that forces acid across the protective gastric mucosa. In the 1970s, benzimidazoles were discovered as powerful antiseretory compounds without acute toxicity and quickly became lead compounds in the search for treatments of various GI conditions. Timoprazole, a benzimidazole, was developed and discovered to have inhibitory effects on acid secretion. It was the precursor to Omeprazole, and in 1977, picoprazole, another benzimidazole predating omeprazole, was first synthesized. In 1978, the first priority product patent was filed in Sweden by Haessle, a daughter company of AstraZeneca, for pharmaceutical preparations and method for inhibiting gastric acid secretion, indicating that substituted benzimidazoles inhibit gastric acid secretion by blocking the gastric proton pump. Modifications of the unstable ester of picoprazole led to omeprazole in 1979.\textit{In vitro} and\textit{in vivo} studies performed in humans, pigs, and rabbits later confirmed the therapeutic effects. In 1985, Haessle Labs, Sweden, worked on developing oral formulations of Omeprazole. Omeprazole was first marketed in the United States in 1989 by Astra AB, now AstraZeneca. An over-the-counter brand, Prilosec OTC, is available in the US for treatment of heartburn. It is now also available from generic manufacturers under various brand names. Omeprazole is one of the most widely prescribed drugs internationally. It is on the World Health Organization’s Model List of Essential Medicines. The origin of omeprazole is a somewhat atypical story of primarily being engendered from the efforts of one sector, but also exemplifies the productivity of pharma company screening programs of candidate compounds for common conditions that nonetheless qualify as unmet medical needs.\textsuperscript{87,88,89,90,91,92,93}

\textsuperscript{85} Lock et al., From toxicological problem to therapeutic use: The discovery of the mode of action of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohaxanedione (NTBC), its toxicology and development as a drug. J. Inher. Metab. Dis. 1998; 21: 498-506
\textsuperscript{86} Lindstedt et al., Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. The Lancet 1992; 340(8823): 813-17
\textsuperscript{87} Zajac, P et al., An overview: current clinical guidelines for the evaluation, diagnosis, treatment, and management of dyspepsia. Osteopathic Family Physician 2013; 5(2): 79-85
\textsuperscript{88} Olbe L, Cederberg C, Ekenved G, Lind T (June 1982) "Antisecretory effects of omeprazole in healthy subjects") – presented at Symposium on Substituted Benzimidazoles
\textsuperscript{89} Klinikum Bayreuth, W. Germany, June 1990 – performed study on 201 patients with peptic ulcers or reflux oesophagitis.
\textsuperscript{91} See Sneader (2005)
\textsuperscript{92} See Reichert and Milne (2002)
\textsuperscript{93} See Zycher et al. (2008)
Onabotulinumtoxin A is derived from Botulinum toxin, a protein and neurotoxin produced by the bacterium Clostridium botulinum, and is used to treat pain and numerous neuromuscular conditions. In 1897, Emile van Ermengem found that botulin toxin was produced by a bacterium, which he named Clostridium botulinum; Justinus Kerner, a physician, first conceived a possible therapeutic use of botulinum. In the late 1960s, Alan Scott, MD, a San Francisco ophthalmologist, and Edward Schantz were the first to work on a standardized botulinum toxin preparation for therapeutic purposes. Scott set up his own company, Oculinum, in Berkeley, CA. By 1973, Scott was using toxin type A (BTX-A) in monkey experiments, and received permission from the FDA in 1977 to test botulinum neurotoxin in humans. Among the early patents, there was one comprising botulinum toxin A (BOTOX) for the parenteral treatment of migraine headaches. Named inventor Dr. William Binder is president of Miotech and a consultant to Allergan. In 1991, a priority method of use patent application was filed in the UK by Allergan, which acquired originator Oculinum in 1989. Other botulinum neurotoxin drugs are under development at Tokushima University in Japan. Botulinum toxin A is launched all over the world for dozens of indications. As of February 2014, there are over 100 use and process patents issued in the US and Europe covering various indications, including the treatment of chronic migraine, overactive bladder and hyperhidrosis. Outside of US, there are at least 20 indications within 83 countries. This is yet another example of research starting in the public sector that was transformed into private sector enterprises with original inventors starting their own companies.\(^{94}\)

Propofol is a short-acting, intravenously administered hypnotic/amnestic agent. Its uses include the induction and maintenance of general anesthesia, sedation for mechanically ventilated adults, and procedural sedation, with recovery that is more rapid than with barbiturates and can be combined with use of opioids for pain. The original study on its preparation was published by AJ Kolka in 1956, and Ecke & Kolka transferred the US patent in 1958 to Ethyl Corp. Anesthetic activity of ICI-35838 was first observed in mice in May 1973, and lead to the discovery of the compound that later became propofol in the Biology Department of ICI Pharmaceuticals Division, aka Imperial Chemical Industries Plc. (Now AstraZeneca). In 1977, Dr. Brian Kay with Prof. Rolly in Belgium conducted the first clinical trial in patients with a formulation containing 2% propofol in 16% cremophor and 8% alcohol. Another US preparation patent assigned to Universal Oil in 1984. In 1986, this intravenous hypnotic was released for clinical use in adults for induction and short-term maintenance of anesthesia as propofol. Expanded indications for sedation of adult patients in ICUs in early 1990s, and later expanded to labeling for the pediatric setting. In February 1998, the US issued a patent covering the new microbial-resistant formulation of propofol, which expires in 2015. Propofol is also commonly used in veterinary medicine. Propofol is approved for use in more than 50 countries. It is on the World Health Organization’s List of Essential Medicines. Originally marketed as Diprivan by AstraZeneca, it is now sold generically by various companies in many parts of the world. The story of propofol continues the theme of drug companies pursuing screening programs for candidate drugs to address apparent areas of unmet need and providing the resources in terms of funding and/or investigative compounds to clinical research at AMCs.\(^{95}\)

\(^{94}\) Truong D, Dressler D, Hallett M. Manual of Botulinum Toxin Therapy. Cambridge, UK: Cambridge University Press; 2009
\(^{95}\) http://www.sivauk.com/joom/images/stories/york/abstracts/Propofol.pdf
Remifentanil is a potent ultra short-acting synthetic opioid analgesic drug. It is given to patients during surgery to relieve pain and as an adjunct to an anesthetic. Remifentanil is used for sedation as well as combined with other medications for use in general anesthesia. In 1983, at American Critical Care (Illinois), two studies were conducted and later described that the addition of an ester group to drugs can result in rapid clearance. In 1991, Glaxo Research Laboratories described the process of incorporating an alkyl ester to analgesics to make them more susceptible to being metabolized rapidly. In 1991, Glaxo Research Laboratories described the ability of remifentanil to inhibit electrically evoked contractions in guinea pig ileum as well as rat & mouse vas deferens, and noted that its inhibitory effects are mediated through the mu-opioid receptor in all tissues tested. In 1992, Glaxo Research Laboratories confirmed that remifentanil had similar hemodynamic effects as other mu opioid agonists, but that the effects were more short-lived (considered a positive attribute in this case). In 1993, Glaxo Research Laboratories and the University of Illinois, Chicago conducted a study in dogs that reported the cardiovascular and cerebral effects of remifentanil and alfentanil (another analgesic) as being similar, but remifentanil was short-acting. In 1993, Glaxo Research Laboratories, Duke Medical Center, University of Utah, Stanford University, McGill University collaborated on small human studies to examine pharmacokinetics and pharmacodynamics of remifentanil; demonstrating its short half-life in humans compared to other analgesics. It was approved as a general anesthetic in 1996 in the US by GSK and soon launched in Europe as well. In 1999, Abbot acquired parts of Glaxo’s anesthesia business in USA, including remifentanil. By 2000, it had been launched in 64 countries and is marketed by GlaxoSmithKline and Abbott (as Ultiva). The derivation of this drug like others in this review came about from screening programs at drug companies acting in concert with research programs at AMCs.

Rituximab is a recombinant chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of immune system B cells. Rituximab destroys B cells and is used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells, such as lymphomas, leukemias, transplant rejection, and autoimmune disor-

97 Carl Resc (1999). Anesthesia & Analgesia. 89(4S)
In 1975, MRC Laboratory of Molecular Biology in the UK performed one of the first studies outlining the production of the monoclonal antibody. In 1975, NCI-funded research produced antibodies that target one specific protein (i.e., monoclonal and polyclonal antibodies). The first test of this treatment occurred in 1980 in a patient with non-Hodgkin lymphoma (NHL), which resulted in the award of a Nobel Prize in 1984. During the same period, Sidney Farber Cancer Institute and Harvard Medical School conducted the first study to identify the CD20 antigen. Later in 1987, the University of Washington and the Fred Hutchinson Cancer Research Center performed a small human study in which four patients with B-cell lymphoma were treated with a murine monoclonal antibody against CD20. With CD20 identified as a potential antitumor target, IDEC pursued studies to specifically bind to CD20 and eliminate cancerous B cells, and in 1994, published on the generation of a chimeric antibody against CD20 (which eventually became Rituximab) as well as an in vivo study in monkeys where they noted that the CD20 antibody reduced B cells. Clinical development followed rapidly and in 1994, IDEC (now Biogen Idec) began Phase I trial for patients with recurrent B-cell lymphoma; the next year, Biogen Idec and Genentech entered a collaborative agreement for both companies to co-promote Rituximab. It was then approved in the US in 1997 and shortly thereafter the results of the MD Anderson Cancer Center and IDEC primary trial that led to the approval were published. The U.S. patent was issued in 1998 and will expire in 2015.

Rituximab is sold under the trade names Rituxan, MabThera and Zytux. Again somewhat atypically, Rituximab was primarily worked on in the public sector through the basic research and discovery phases and only cooperatively later downstream with the private sector.

Sildenafil citrate is a drug used to treat erectile dysfunction and pulmonary arterial hypertension (PAH). It acts by inhibiting cGMP-specific phosphodiesterase type 5 (PDE5), an enzyme that promotes degradation of cGMP, which regulates blood flow in the penis. In the 1960s, it was discovered that several variants of a peptide enzyme had the effect of relaxing involuntary muscles and PDE5 in kidney tissue inhibits the effect of the peptide. In the 1980s, an active cardiovascular research program at Pfizer led to the development of an antagonist to PDE5, which might have the effect of using kidney function to reduce blood pressure. Lead compounds were sought from the literature and Pfizer settled on unmarketed Zaprinant from Rhone-Poulenc and prepared enhanced

110 Reff et al., Blood. 1994; 83(2): 435-445
113 NCI background on rituximab: http://www.cancer.gov/aboutnci/servingpeople/cancer-research-progress/discovery/blood-cancer
analogue. One of these analogues turned out to be a PDE5-inhibitor, later to become sildenafil citrate. Sildenafil (drug code UK-92,480) was synthesized by a group of pharmaceutical chemists working at Pfizer's Sandwich, Kent, research facility in England (Merck Index reports Prepn EP and US patent assigned to Pfizer in 1992, 1993; SAR study by NK Terrett published in 1996). Sildenafil was discovered as an inhibitor of PDE5 with 100 times the potency of previous product Zaprinast (by Pfizer). By 1993 sildenafil was no longer seen as a promising product for treatment of angina pectoris as Phase I clinical trials under the direction of Ian Osterloh suggested that the drug had little effect on angina. However, these trials found that it could improve symptoms of erectile dysfunction (ED) even in individuals with no established organic cause. Pfizer therefore decided to market it for ED, rather than for angina. The drug was patented in 1996, approved for use in erectile dysfunction by the FDA on March 27, 1998, becoming the first oral treatment approved to treat erectile dysfunction in the United States, and that same year it was marketed in the UK, Germany, France, Australia, Israel and sold as Viagra and under various other trade names. Its discovery is another example of the combination of serendipity and screening programs resulting in the melding of a commercial opportunity with an unmet medical need.

Sumatriptan is a treatment for migraines. One of the most prominent migraine researchers, Harold Wolff, was the first to propose that a cause of migraine headaches was vasodilation. Indeed, in 1938 he found that ergotamine tartrate, a vasoconstrictor, could reduce migraine headache. Studies at Montefiore Hospital in New York City in 1960 found that 5-HT may be useful in the treatment of migraine due to its vasoconstrictive properties. Soon after, work by James Lance at the University of New South Wales supported this observation. His group also discovered that 5-HT excretion increases and plasma serotonin 5-HT decreases during migraine attacks. These studies supported further examination into how the vasoconstriction caused by 5-HT could be utilized as a migraine treatment, and research at Glaxo that focused on the development of an anti-migraine drug began in 1972 under the direction of Patrick Humphrey. Around the same time, Pramod Saxena at Erasmus University published work that detailed how methysergide, which initially was thought to be a 5-HT receptor antagonist, caused vasoconstriction in the brain without changing blood pressure. Glaxo researchers repeated this result and eventually discovered a previously unknown 5-HT

116 Matsunaga K1, Furchgott RF, Interactions of light and sodium nitrite in producing relaxation of rabbit aorta. *J Pharmacol Exp Ther.* 1989; 248(2): 687-95
122 See Sneader (2005)
123 See Zycher et al. (2008)
receptor that was activated by methysergide. As a result, they began to characterize a number of serotonin receptors with the goal of identifying a receptor that could be selectively activated in order to reduce the symptoms of migraines without negative side effects such as cardiovascular issues. They ultimately found that activation of the 5-HT1 receptor was the best candidate, and developed analogues of serotonin that selectively activated this receptor. This led to development of the drug that would become sumatriptan, which selectively activates the 5-HT1 receptor and causes constriction of cranial, but not peripheral, blood vessels. While further probing into the mechanism of action of sumatriptan, Glaxo researchers relied upon a number of publicly-funded research groups to aid them in better characterizing the drug. For example, research at Mass General Hospital and the Mayo Clinic found that sumatriptan could induce vasoconstriction by causing a reduction in the levels of CGRP (calcitonin gene-related peptide), a molecule that causes vasodilation and migraine pain. Sumatriptan was approved for the treatment of migraine and marketed as Imitrex by Glaxo in 1991. Ultimately, the development of sumatriptan was largely a result of a Glaxo screening program; however, Glaxo’s success was dependent upon the results of concurrent, publicly-funded research.124,125,126,127,128,129,130,131,132,133,134

Tamsulosin is used in the treatment of difficult urination, a common symptom of benign prostate enlargement, or BPH. Tamsulosin and other medications in the class called alpha blockers (α-blockers), work by relaxing bladder neck muscles and muscle fibers in the prostate itself and made it easier to urinate. Initial treatment plans for BPH were begun in the 1960s and 1970s when studies suggested a role for α-blockers and hormonal therapy. In 1976, Caine and associates reported on the efficacy of α-blockers for the treatment of BPH. In 1985, Yamanouchi published a paper describing a thorough characterization of tamsulosin. It showed its activity as a potent α-1 antagonist in animals, as well as its ability to antagonize noradrenaline induced contractions in rats. In 1986, Yamanouchi researchers demonstrated that the R-enantiomer is 50-141 times more potent than the S-enantiomer at blocking α-1 adrenoreceptors in rabbit lower urinary tract and prostate. Further work on isomers and racemates were published by Yamanouchi researchers in 1987, while HPLC determination from plasma was published in 1990. Also in 1990, Hamamatsu University first published reports of clinical trials of tamsulosin in humans for BPH, indicating that it is use-

129 Curran, Hinterberger, and Lance et al., Brain 2965; 88(S): 963-962.
ful in the treatment of BPH. The next year, studies reporting minimal side effects and specificity of the therapeutic effect were published, demonstrating the safety and effectiveness of tamsulosin in treating BPH in humans. It was introduced in the Japanese market in 1993. Although developed by Yamanouchi Pharmaceuticals Co., Ltd, (now part of Astellas) by agreement with Boehringer Ingelheim Pharmaceuticals Inc. (BIPI), the product is sold under the brand name Flomax, and obtained marketing approval in 1997 in the US. Flomax is available generically and is marketed all over the world. Yamanouchi’s vigilance for promising applications of alpha-blockers combined with providing the resources for trial work in the public sector appear to have been primarily responsible for Flomax.  

Zidovudine or azidothymidine (AZT) is a nucleoside analog reverse-transcriptase inhibitor (NRTI), which inhibits the enzyme (reverse transcriptase) that HIV uses to synthesize DNA, preventing the formation of viral DNA, and can also prevent some forms of HIV transmission (i.e., mother-to-child). In the 1960s, Nobel prize-winning research showed that avian cancers were largely caused by retroviruses. Around the same time, AZT was first synthesized in 1964 under an NIH grant as a potential drug for leukemia. Basic research on leukemogenic tumor retroviruses in animals led to the discovery of reverse transcriptase by two separate groups at the University of Wisconsin and MIT. In the mid-1970s, German scientists reported that AZT inhibited a retrovirus, and in 1983, scientists in France isolated HIV and determined that it was a retrovirus. In 1984, Burroughs Wellcome began the search for drugs that would attack retroviruses. AZT was one out of fourteen chosen for screening. From 1980-1987, reverse transcriptase inhibitors were tested for HIV at NCI after having been tested as potential cancer drugs earlier. Most of the work on zidovudine was done in collaboration by NCI and GSK. Many early trials of zidovudine were terminated prematurely because of significant improvement in survival observed early on, and AZT and antiretroviral therapy had a major impact on achieving control of the HIV-1/AIDS pandemic. AZT received FDA approval in 1987 and was marketed by GSK as Retrovir. By 2005 the patent had expired, and FDA has since approved four generic forms of AZT for sale in the U.S. AZT was the first US approved treatment for HIV, and the first breakthrough in AIDS therapy. In November 2009, GlaxoSmithKline formed a joint venture with Pfizer which combined the two companies’ HIV assets in one company called ViiV Healthcare. This included the rights to zidovudine. HIV may become AZT-resistant over time, and therefore AZT is now usually used in conjunction with other anti-HIV drugs in the combination therapy called highly active antiretroviral therapy (HAART) (i.e., AZT is included with Combivir and Trizivir). AZT is included on the World Health

137 Honda K, Nakagawa C Alpha-1 adrenoceptor antagonist effects of the optical isomers of YM-12617 in rabbit lower urinary tract and prostate.” J Pharmacol Exp Ther. 1986 Nov; 239(2): 512-6
Organization’s Model List of Essential Medicines. Much of the basic research and discovery work was done in the public sector but GSK’s screening program certainly accelerated the pace of development.\textsuperscript{141,142,143,144,145,146,147,148}

**Classes**

**ACE Inhibitors**

This term refers to their properties as angiotensin converting enzyme (ACE) inhibitors. The first-in-class compound was captopril (Capoten). Other notable ACE inhibitors are: perindopril, enalapril, lisinopril, ramipril. These are primarily oral agents for the treatment of hypertension & heart failure. Briefly, their mechanism of action derives from the fact that the renin-angiotensin system (RAS) regulates many physiological functions, including hypertension. Angiotensinogen, a glycoprotein, is released from the liver and cleaved by the enzyme renin to form angiotensin I (ANG I). ANG I is activated to angiotensin II (ANG II) by angiotensin converting enzyme (ACE). ANG II then acts on specific receptors to induce various changes. One of the main effects of ANG II is blood vessel constriction, which can cause high blood pressure. ACE inhibitors prevent ANG II production, resulting in a decrease in blood pressure. In the 1960s, John Vane at the Royal College of Surgeons of England showed that extract from the venom of the Brazilian arrowhead viper could serve as an ACE inhibitor. In the 1970s, Miguel Ondetti et al at Squibb isolated peptides from the Brazilian arrowhead viper venom. One, teprotide (already isolated by Vane) was synthesized and tested at Squibb. Teprotide was an effective anti-hypertensive by IV, but ineffective orally. In 1973, Byers and Wolfenden, at the University of North Carolina (supported by the NIH) performed studies that allowed the Squibb team to synthesize additional binding compounds for ACE. The resulting compound from this research was not potent enough, so Squibb researchers continued experimenting with further approaches and eventually found that replacement of the carboxyl molecule group with thiol allowed for an increase in captopril activity. Bristol-Myers Squibb was granted a patent in 1977 in the US. Captopril was approved by the FDA in 1981 for patients responding poorly to other therapies for severe hypertension and for patients on multidrug regimens. This appears to be

\textsuperscript{142} Baltimore, MIT. *Nature*. 1970; 226(5252): 1209-11
\textsuperscript{143} Poiesz et al. *PNAS* 1980; 77(12):7415-9
\textsuperscript{144} Mitsuya et al. *PNAS* 1985; 82(20): 7096-7100
\textsuperscript{145} Yarchoan et al. *The Lancet* 1986; 327(8481): 575-80
\textsuperscript{146} Broder, The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. *Antiviral Res*. 2011; 85(1)
\textsuperscript{147} See Reichert and Milne (2002)
\textsuperscript{148} See Zycher et al. (2008)
another example of company screening programs picking up some promising leads from the basic research available in the public sector on population-wide health problems and facilitating public sector research until a candidate drug emerged.\textsuperscript{149,150,151,152,153,154,155,156,157,158}

**Anti-VEGF agents**

The first observations that increased vascularity can occur during tumor growth were made over 100 years ago. However, discoveries that led researchers to believe that tumor growth requires new blood vessel formation were not made until the mid-twentieth century (see references \textsuperscript{155} and \textsuperscript{156} for full review). Warren Lewis at Johns Hopkins University (1927), Gordon Ide at the University of Rochester (1939), and Glenn Algire at the National Cancer Institute (1945) all published important studies that described tumor-associated increases in vascularity and, in the case of Ide's and Algire's groups, noted that angiogenesis is critical for tumor growth. While several studies indicated that tumor cells themselves may produce a factor that promotes angiogenesis, it was not until 1971 that Judah Folkman at Harvard Medical School suggested that inhibition of angiogenesis may be a viable anti-cancer therapy. Folkmann and others sought then sought to inhibit this process and identify a tumor-secreted pro-angiogenic factor. After several failed attempts to identify this factor, the discovery of vascular endothelial growth factor (VEGF), a secreted factor that promotes endothelial cell growth, was made by Napoleone Ferrara while at Genentech in 1989. Though Ferrara’s discovery of VEGF occurred while he was working on a cardiovascular project, he chose to take advantage of Genentech’s policy that allows employees to set aside time for personal research interests in order to probe into the role of VEGF in cancer. In 1993, Ferrara’s group demonstrated antibody-mediated VEGF inhibition could reduce the growth of mouse tumors, and in 1997 they published a study describing a humanized form of the anti-VEGF antibody that eventually became to be known as bevacizumab (Avastin). Bevacizumab was approved by the FDA in 2004 for treatment of patients with metastatic carcinoma of the colon and rectum in combination with chemotherapy. Therefore, while early, publicly-funded studies established the concept that angiogenesis is a critical aspect of tumor growth and a potential anti-cancer target, private research led to the discovery

\textsuperscript{150} Byers LD, Wolfenden R. Binding of the by-product analog benzylsuccinic acid by carboxypeptidase A. *Biochemistry* 1973; 12(11): 2070-78
\textsuperscript{151} Maxwell & Eckhardt, Drug Discovery: A Casebook and Analysis. Pg.19-34
\textsuperscript{152} See Sneader (2005)
\textsuperscript{153} Scriabine, “Discovery and Development of Major Drugs Currently in Use,” pg.187
\textsuperscript{154} Patchett, “Enalapril and Lisinopril,” 3:129-37
\textsuperscript{155} Lednicer, New Drug Discovery and Development, 50-51
\textsuperscript{156} Turk, “Targeting Proteases”
\textsuperscript{157} See Reichert and Milne (2002)
\textsuperscript{158} See Zycher et al. (2008)
of both the pro-angiogenic factor and a method to target its activity in a manner suitable for the clinic.\textsuperscript{159,160,161,162,163,164,165,166,167,168,169,170}

**Bisphosphonates**

The first synthesis of bisphosphonates occurred over a century ago, and their uses in the 19th century were primarily industrial. It was often used as an anti-scaling agent due to its ability to inhibit the precipitation of calcium carbonate. In 1966, studies led by Herbert Fleisch at the Schweizerisches Forschungsinstitut and the Institute Dr. R Straumann in Switzerland found that inorganic pyrophosphate inhibited both the dissolution and precipitation of calcium phosphate. Further research confirmed that pyrophosphate was an endogenous regulator of calcification and bone mineralization. When researchers sought to determine whether administration of pyrophosphate could alter mineralization, bone resorption, and prevent the calcification of soft tissue, their efforts were largely unsuccessful. This was attributed to the enzymatic destruction of the exogenous pyrophosphates. Eventually, it was found that the bisphosphonates could have many of the same effects of endogenous pyrophosphate without being destroyed during administration. These results suggested that bisphosphonates could be used therapeutically to regulate calcification and bone mineralization. These studies, led by Fleisch and R. Graham Russell, were primarily performed at the University of Berne, Switzerland and the Laboratory for Experimental Surgery in Davos, Switzerland in collaboration with M.D. Francis from Proctor & Gamble. Proctor & Gamble supplied Fleisch with a number of their bisphosphonates in order to test their properties and effects on bone resorption. This collaboration was considered critical for the early studies of bisphosphonates. In 1969 and 1971, Fleisch et al went on to demonstrate that bisphosphonates could improve osteoporosis in rats. Around this time, Fleisch was contacted by a physician regarding a patient with myositis ossificans progressiva, in which soft tissue undergoes calcification. Fleisch helped arrange for the bisphosphonate etidronate, which was being synthesized at Proctor & Gamble, to be given to the patient. The patient's condition improved dramatically. The success of this intervention led

\textsuperscript{159} Ferrara, VEGF and the quest for tumour angiogenesis factors. *Nature Reviews Cancer*. 2002; 2:795-803

\textsuperscript{160} Ferrara et al., Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. *Nature Reviews Drug Discovery* 2004; 3:391-400:


\textsuperscript{162} Ide AG, Baker NH, Warren SL, Clark ER, Clark EL, A starting point. *Am. J. Roentgenol.* 1939; 42: 891–899

\textsuperscript{163} Algire et al. *J. Natl Cancer Inst.* 1945 ; 6: 73–85


\textsuperscript{168} Goodman, *J. Clin. Invest.* 2004; 113(7): 934


researchers to believe that etidronate could be used for other bone disorders. It was studied in the context of Paget’s disease, which is characterized by accelerated bone resorption and formation. This use of etidronate was successful, and it was eventually approved in 1977 and marketed as Didronel. In the years that followed, a number of bisphosphonates were studied in the context of and approved for other bone disorders such as osteoporosis. Overall, while the concept that bisphosphonates could be used as a therapy for bone disorders began in publicly-funded laboratories in Switzerland, collaborations with industry were absolutely critical for the development of the drugs that were eventually approved.171,172,173,174,175,176,177,178,179

**HIV Protease Inhibitors**

In 1983, two separate studies from the Institut Pasteur in France and the National Cancer Institute were published that detailed the identification of the virus that causes AIDS. Research on this virus, eventually termed HIV, began soon after its initial discovery in order to identify a mechanism by which it could be therapeutically targeted. In 1985, the HIV nucleotide sequence was released in two separate publications, one from the Institut Pasteur and one from a collaborative effort between the National Cancer Institute, Harvard Medical School, and Centocor (now Janssen Biotech). These results were critical for ongoing research into how to target the virus. Between 1988 and 1990, a number of discoveries were made relating to the protease of the HIV virus. Merck was among the first to demonstrate that the HIV protease is required for viral infection. Collaborative efforts between Upjohn (now Pfizer) and the NIH confirmed these results. Altogether, these studies provided evidence that the HIV protease was a viable drug target for antiretroviral therapy. Merck published the first crystal structure of the HIV protease in 1989, and a more accurate structure was published in 1990 by the NCI and the California Institute of Technology. HIV treatments available at the time (nucleoside reverse transcriptase inhibitors) were not by themselves largely successful in treating patients. Therefore, a number of labs utilized the HIV protease structural data in order to pursue rational drug design methods to identify compounds that could inhibit the enzyme’s activity. Roche utilized computer-led rational drug design to develop saquinavir, and in 1991 published results that

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171 Russell RGG, Bisphosphonates: The first 40 years. Bone 2011; 49(1):2-19
178 Bassett et al The Lancet 1969; 294(7625): 845
179 Smith (et al). Lancet 1:945-947
supported the ability of saquinavir to inhibit the HIV protease. After demonstrating in a number of trials that saquinavir was effective in HIV patients when used in combination with other antiretroviral therapies, it was approved by the FDA under an accelerated pathway in 1995. A number of other HIV protease inhibitors were developed in the following years. While these inhibitors were developed by the private sector, their development was dependent upon initial discoveries made by a combination of publicly- and privately-funded research.\textsuperscript{180,181,182,183,184,185,186,187,188,189,190,191}

**Interferons (beta-1b, beta-1a)**

Interferons are proteins produced by the immune system in response to the presence of tumors and foreign agents. Three classes of interferons have been discovered (alpha, beta, gamma). They have a wide variety of physiological effects: antiviral, anti-angiogenic, cell growth inhibitory, and immunoregulatory. Interferons are used for a wide variety of indications (hepatitis C, cancer, multiple sclerosis, etc.) In the 1950s, researchers at the National Institute for Medical Research in London discovered interferons and that they increase resistance to viral infections. In the 1970s, a method to purify interferons was developed through NIH research, and in 1974 interferon alpha was purified. Amino acid analysis was carried out in 1979, permitting cDNA to be cloned and expressed in bacteria, which made commercial production feasible. Synthesis of interferon beta-1b was accomplished in 1980 by the Triton subsidiary of Shell Oil (later acquired by Berlex Biosciences), and manufactured by Chiron. Pharmacological testing of interferon beta-1b was begun in 1982 with expression, purification and characterization reported in 1984. However, production on a scale sufficient for clinical usefulness required genetic engineering, a process developed by researchers at Biogen, Genentech, and Roche. Two interferon genes were recombined into a hybrid interferon, and Interferon beta-1b was approved in the US in 1993, and launched in the mid-1990s in the US and Europe, with biosimilars (e.g., CinnoVex, CinnaGen) now available outside the US. Interferon discovery and development appears to have significant overlap between the two sectors with

\textsuperscript{181} Gallo et al. *Science* 1983; 22(4599): 865-7
\textsuperscript{182} Wain-Hobson et al. Nucleotide sequence of the AIDS virus, LAV. *Cell* 1985; 40: 9-17
\textsuperscript{185} Ashorn et al. *PNAS* 1990; 87(190): 7472-76.
\textsuperscript{188} Wlodawer et al. *Science* 1990; 245: 616-21
\textsuperscript{191} Wensing et al. *Antiviral Research* 2010; 85:59-74.
working out the challenges of commercial production being the province of the private sector. 192,193,194,195,196,197,198,199,200,201,202

**TNF-blockers**

While the concept that the body may produce an endogenous factor that is toxic to cancer cells had been discussed for more than one hundred years, tumor necrosis factor-alpha (TNF-alpha) was not discovered until 1975 at Memorial Sloan-Kettering Cancer Center in the laboratory of Lloyd Old. In the years that followed, it was found that TNF-alpha was produced by macrophages and could cause cancer cell lysis, and early studies thus sought to demonstrate whether TNF-alpha could serve as an anti-cancer agent. It was eventually cloned by Genentech in 1984, which allowed for larger-scale studies on its effects on cancer cells. At the same time, the laboratory of A. Cerami identified cachetin at Rockefeller University in the 1980s. This molecule was found to promote a “wasting” phenotype common to infectious diseases and cancers. In 1985, the Cerami Lab, in collaboration with Hoffman-La Roche and the Scripps Clinic & Research Foundation, found that TNF-alpha and cachetin were the same molecule. This was one of the first indications that TNF-alpha may not be a viable anti-cancer agent, as cachetin was deemed harmful to patients. Indeed, the Cerami Lab eventually demonstrated that TNF-alpha could induce massive inflammatory responses such as sepsis, leading researchers to believe that targeting this molecule would be beneficial for sepsis and autoimmune diseases. In the late 1980s, several studies were performed that examined the effects of blocking TNF-alpha in vivo, and in 1993, collaborative work was published from Centocor (now Janssen) and the Vilcek Lab at the New York University School of Medicine that described a monoclonal antibody with high affinity and specificity for human TNF-alpha. This monoclonal antibody, known as infliximab (Remicade), was studied as a treatment for Crohn’s Disease in the early 1990s. It was approved for Crohn’s in 1998, with approvals for several other indications (such as rheumatoid arthritis and psoriasis) following soon after. Several other TNF alpha blockers, such as etanercept

196 See Reichert and Milne (2002)
197 See Zycher et al. (2008)
198 See Sneader (2005)
199 Pieters, Interferon, 147-87
200 Isaacs and Lindenmann, “Virus Interference. I. The Interferon”
(Enbrel), were approved and marketed shortly after Remicade. Overall, both the identification of TNF-alpha as a target for autoimmune disease and the development of its targeting therapies were the result of a number of collaborations between the private and public sectors.\textsuperscript{203,204,205,206,207,208,209,210}

\section*{Combinations}

\textbf{Combined fluticasone and salmeterol}

The combination of fluticasone (a corticosteroid) and salmeterol (a long-acting beta receptor agonist) is used to control symptoms of asthma and improve breathing. Studies performed in the mid-twentieth century brought corticosteroids and beta receptor agonists to the spotlight with regard to asthma treatment. In the 1950s, several discoveries were made that demonstrated that inhaled corticosteroids could be used as an anti-inflammatory therapy to improve breathing in asthmatic patients. In the 1960s, the bronchodilating effects of short-acting beta receptor agonists such as salbutamol were published by Allen and Hanbury’s, which was part of Glaxo. Inhaled salbutamol was later marketed by Glaxo as Ventolin. In 1972, Allen and Hanbury’s launched the first inhaled steroid for asthma (beclomethasone), and a number of inhaled steroids for asthma treatment have been developed since. In 1988, Glaxo-supported research at the Sahlgrenska University Hospital in Sweden found that the long-acting beta receptor agonist salmeterol could improve asthma symptoms in patients, and it was later approved by the FDA for the treatment of asthma in 1994. Shortly after its approval, a number of Glaxo-supported clinical studies were published detailing that combination salmeterol and corticosteroid treatment resulted in positive outcomes for asthma patients over corticosteroid treatment alone. The FDA approved Glaxo’s Advair Diskus, an inhaled combination of fluticasone and salmeterol, in 2000. Though the patent protection for Advair expired in 2010, it has been extremely difficult to replicate by generics companies and it remains the only combined

\begin{thebibliography}{99}
\bibitem{208} Cerami, J Intern Med 2011; 269(1): 8-15
fluticasone and salmeterol treatment on the market. In general, the development of these two drugs and the studies demonstrating that they were effective when used in combination were largely performed or funded by the private sector. 211,212,213,214,215,216,217

211 McKeage and Keam, Drugs 2009; 69(13):1179-1960
212 Sanders M, Inhalation therapy: an historical review. Primary Care Respiratory Journal 2007; 16(2): 71-81
213 Ullman et al. Thorax 1988; 43(9): 674-78