

Chapter 00: Introduction

What medicines you will need & why you might not ever have them

“Big Pharma” has not had any financial losses; however, it has been closing research divisions and laying off very qualified and experienced people who were working on the drugs for your future. The investment society has made in educating these individuals, who found once prestigious well-paid jobs in pharma, is now unproductive. After being laid off, some of these scientists are taking their pet projects to existing biotech and to venture capitalists in order to try and set up their own biotech companies. This is by no means easy, as you will find out while reading this book.¹

Meanwhile, cash-rich Big Pharma has been buying back stock to prop up its stock prices, and Wall Street and company directors appear to approve of this. CEOs that did not participate in this buyback were suddenly “departed” from their jobs.

This means that society will not have many of the medicines it needs, when it needs them.

Aging is the major risk factor for disease

The population is becoming older, and with aging comes an increase in debilitations, such as diabetes, obesity, cancer, pain, cardiovascular disease, osteoporosis, and Alzheimer’s disease (AD).² In the past, the pharma system was relied on to develop drugs to meet society’s needs. Within huge caveats about price and availability, the market has worked in many ways.

1 In this book we give many details, which we hope are easy to follow for nonscientists and nonphysicians. For this introduction we might say “diabetes” when we mean “type 2 diabetes mellitus.” The word mellitus is often dropped in literature, but it is an extremely important distinction. It means the urine, or “siphoned fluid,” is sweet; the much rarer “diabetes insipidus” means that the urine is lacking in taste. Yes, there was a time when physicians tasted the urine of people who urinated too much.

2 And other neurodegenerative disorders.

Pharma and biotech are still working on many diseases, but they have given up on too many of them because they are deemed too difficult. Of those listed previously, pharma is investing quite reasonably by pursuing better medicines for cardiovascular disease and osteoporosis; collectively, it is probably spending enough.

It is spending more and working most avidly on cancer and diabetes, with or without obesity. It is also working diligently on some so-called orphan or rare diseases that have relatively few sufferers.

The difficulty with cancer drug development is that many of the drugs make people feel sicker and only extend life by a few months. The new drugs are also very expensive. Despite this, treatment options have improved a great deal in the developed world. Now, obesity drug candidates have been failing because they seem to make patients feel suicidal. Diabetes drugs are proving to be profitable to pharma. One fairly new class of medicines has produced three approved drugs against diabetes in the last 6 years and we have identified 34 other candidates trying to compete with these three. Imagine the amount of money spent developing 34 drugs. If they all worked and were approved, the total investment could be easily \$30-60 billion. Unless one of them is an oral pill that can be administered once per week, there will be no “market access.”³ The existing drugs will be too good and too similar. These 34 drugs target one and the same receptor. There are 30 targets known for diabetes, and there are over 300 diabetes projects. If these are to reach approval, then with each drug costing an estimated \$870 million in “out of pocket” expenses and \$1.8 billion including capitalized costs, this would total more than \$270-550 billion. This money is not being spent on innovative new drugs, but mostly on so-called “me-toos.”⁴ Of course, this money will not all be spent because between 90 and 99% of drug-development projects fail or

³ Market access is one of the newish terms used by pharma consultants to describe the phenomenon that an approved drug will not necessarily become a prescribed, used, profitable drug if it is number 5-15 in its class.

⁴ Me-toos are drugs that are similar in structure and mechanisms of action to already available drugs, usually from competitors.

are dropped. Many are dropped because a competitor dropped a similar drug, targeting the same target, while others are found to be unsafe or not efficacious.

The remaining two age-related diseases on the list, pain and AD, are hardly being worked on at all. Another newly neglected, in terms of drug development, disease is schizophrenia, which can affect someone from age 20 onward and is arguably more debilitating to the individual than AD. Still, there are many more diseases that should be addressed.

Painful truth & AD

Some companies are working on inflammatory pain, which brought the very efficacious and perceived as very safe Vioxx and Celebrex to market. Vioxx has been subject to many lawsuits since it was found to contribute to cardiovascular incidents that accelerated death in some patients. Merck, which developed the drug, was, in some aspects, allegedly found guilty of being economical with the truth. Pfizer, which developed Celebrex, has now been found by inference⁵ to have lied to the FDA⁶ about its heart attack data.⁷ The irony—if something can be called ironic when patients have died—is that both drugs are probably safe provided they are given to the right patients and they take them at the right dose. The proper selection of patients for clinical trials and treatment is strongly featured in this book.

The type of pain we are referring to is resistant to morphine, which is still the best pain killer known, despite being around for 5,000 years. Drug-development programs for this “neuropathic pain” have been largely abandoned by pharma.

AD is predicted to become an epidemic. Already more people suffer from it than have HIV/AIDS. As more and more people become older, the

5 We are not qualified to interpret legal data directly, but the payment of a “fine” could be said to imply compliance or agreement with the accusation or simply represent a concession that the case was not worth fighting. We are not stating any opinion about any drug company being found “guilty,” even if reportedly found guilty by any judicial system.

6 The U.S. Food & Drug Administration, which oversees safety and, to a somewhat lesser extent, efficacy of both new and existing drugs.

7 See also Chapter 03.

number of victims is likely to soar, with half of those over 85 having it. This will place a great strain on families and healthcare services, and both their budgets. Families make sacrifices that often mean their contribution to the economy is reduced. Full-time care for individuals requires at least three staff members working 8-hour shifts. It will be a strain on the healthcare system; it is not a sector of the workforce that should be growing so significantly. AD will claim the lives of 10 million baby boomers in the next few decades.

George Vradenburg, co-founder and chairman of USAgainstAlzheimer's (USA2), makes compelling arguments. His estimates are that the United States is only spending \$400 million on research on the disease, yet is spending \$200 billion on care, which he compared to Jonas Salk deciding to invest in leg braces for polio patients instead of looking for a vaccine. The projected cost of care by 2050 would be \$1 trillion. Research spending is insignificant compared with the cost burden. We agree with his estimate that at least \$2 billion in annual research on the disease is needed.

Pharma still has some clinical trials running, but the prospect of finding a drug that slows AD progression significantly appears slim. Today, in the face of failing trials, pharma is closing AD drug-development programs because they are too expensive and take too long.

It is common to blame pharma. They are accused of many falsehoods, but it is not all pharma's fault. They have explored the main lead that science has given them, and it does not appear to be working. Some candidate AD drugs have reduced amyloid deposits in the brains of mouse models and improved or even reversed cognitive decline, but while they may decrease the amyloid load in AD patients they have little or no effect on cognitive abilities. Science is not providing enough drug targets; more research investment needs to be encouraged and, actually, demanded if we are to combat AD.

Governments, notably the U.S. government through the National Institutes of Health (NIH), have backed research initiatives in the past. For example, the more than 40-year investment costing many billions of

dollars is now bearing fruit in the fight against cancer and many effective drugs have been approved. The massive, compared to AD, annual research budget of \$3 billion for HIV/AIDS, has brought extraordinary progress; a fatal disease has turned into a manageable chronic illness in a period of 25 years. The force of nongovernmental organizations and lobbyists has made sure it is not only the rich who are being treated.

AD is especially difficult, which is exactly why society should be looking for a preventative therapy for which familial AD has the best chance of revealing an effective therapy. Recent events including the start of a trial on familial AD, backed with government dollars, in Colombia vindicate our thesis: the model of drug discovery needs correction and adaptation. Drugs important for society need to be vigorously pursued; government needs to accelerate funding of research more purposefully and be involved in financing drug discovery trials, not just in post-marketing trials for safety. Pharma needs to be encouraged, if not actually coerced, into pursuing society's needs, and must select patients much more carefully.

Society, government, and pharma have to work together for common goals, but the new trial developed to delay the onset of AD in a family (a third of whose members are likely to develop AD at the age of 45) is using two drugs against the same target. The basis of the model is good, but if the trial does not work, the model must be preserved for other drug candidates using other mechanisms of action from other companies. Trying to prevent AD is much more hopeful than trying to reverse it. But a preventative drug, even for an ultimately fatal disease, has to be very clean with only minor side effects.

More government action required

The familial AD trial is scheduled to last 10 years. The drug has already been around since 2006. If the patent is not extended it may expire ~3 years after approval. Competition would probably appear in less than 3 years. Patent extension is possible, but why make it a legal argument? Why not simply extend the patent based upon approvals? While many citizens and healthcare commentators and practitioners like it when

a patent expires and generics appear, society cannot expect pharma companies to invest heavily over a long period without any chance of recuperating their investments. Short patent life spans mean higher prices.

Another effective erosion against exclusivity during the life of a drug's patent comes from off-label use of another drug approved for another condition. A company can be effectively scooped by a drug not actually approved for the condition in question.

"Fiddling" with patent law, while at the same time making it simpler, is not the only incentive that can be used to entice pharma into not abandoning whole research areas. Anything that is projected to reach epidemic proportions should be granted the same privileges as those given to orphan or rare diseases, for example, tax breaks.

If a foreign force was planning to wipe out 10 million baby boomers, no expense would be spared. AD research and drug development need the kind of lobbying practiced by the defense contractors and the HIV/AIDS activists.

The decisiveness & divisiveness of market access

Pharma is not wholly to blame; the people in *control* of pharma are wholly to blame. The "lesion of the status quo" currently becoming infected is caused directly because pharma is turning its back on its traditional role of providing drugs for society's needs.

Pharma is completely under the control of finance and marketers. Business is dictating its path. The investors and gurus of Wall Street want to return to pharma's traditional double-digit growth, but it is not going to happen. Wall Street needs to curb its ambitions and marvel at the future inventiveness of pharma to carve out a more modest profit from its science-determined future.

Doctors and scientists used to run pharma. A scientific discovery would, with pharma's expertise, turn into a needed and safe drug. Business mentality has turned the industry on its head. MBAs, economists, financiers, and "marketers" are deciding what to spend money on. It does not matter how good a drug candidate might be, it will be scrapped if marketers decide that the drug will not have sufficient market access.

When whole programs are scrapped, which is now the situation we find ourselves in, the intellectual core of the company is lost. Legendary scientists who discovered drugs that earned companies billions over many years are unceremoniously let go.

It is time society decided that decisions should be made by people who care about society and are qualified to make them.

Government can change the future

Government has always been involved in the business of drug discovery. In the United States and probably in the rest of the world, both political parties support the basic research budget and it has often increased when others were cut. Possibly uniquely, in the United States the government often gives more money to health research than is requested by the NIH. Of course, the two sides of the house may be giving money for different reasons, but they recognize the value of the research both for citizens and for companies.

However, if the NIH really wants to become seriously involved in drug development from discovery of mechanisms through drug candidate design to clinical trials, then it really needs to ask for much more. Scientists in academia do not seem to appreciate how much it really costs to develop a drug. The NIH needs to ask for more and the U.S. government needs to give it in order to fund its National Center for Advancing Translational Sciences (NCATS) initiative. Perhaps the NIH should hire a significant portion of the recently laid off R&D scientists who have immediate and current experience in pharma.

In the past decades, government has already paid for extremely costly but important clinical trials to determine the efficacy and safety of drugs and therapies. These long-term studies involving many thousands of patients are simply not affordable for drug companies. It may also be against their interests. It would definitely take government intervention to compare two or more new drugs in parallel in a single large trial.

In Europe, governments, which through their national healthcare programs pay for most of the drugs prescribed, are beginning to insist

via their regulatory bodies to approve drugs only if they are superior or more cost-effective. In other words, if a new drug is being considered for approval, then it would have to be superior to charge a superior price. This must be a good development. It should, at the same time, encourage better drug development, or at least lower prices for me-toos, and encourage “first in class” innovations instead of me-toos.

Government involvement in drug development may also serve to make drugs available at more reasonable prices. This has been done before.

Not all is doom & gloom

Along with the good news of a trial by Genentech on familial AD, Novartis has recently embarked on a clinical trial, involving 17,200 patients over 4 years, to show that one of its drugs,⁸ already used in other conditions, will exhibit cardiovascular protection. The gamble is brave, but quite rational. The drug is only currently approved for a spectrum of auto-inflammatory diseases including the intriguingly monikered Muckle-Wells syndrome.⁹ If Novartis is able to show cardiovascular protection, then the drug will go from near orphan status to mega-market. It is also brave because even if successful, it would need some extension of patent time to make it worthwhile.

Meanwhile, Novartis too is cutting research and laying off highly trained successful drug developers.

What can society do?

We hope this book gives the background and foreground for what the problem is and what the solutions are for developing cost-effective drugs. A major issue being debated here is that if Wall Street and financial considerations are the sole determinants of which medicines pharma chooses to develop, without taking into prime consideration society’s needs, then society, including governments, investors, and pharma

8 canakinumab (Ilaris).

9 Named after Thomas James Muckle and Michael Vernon Wells, who described it in 1962. It is an autosomal dominant disease that causes sensorineural deafness, recurrent hives, fever, chills, and painful joints.

executives, will not have the medicines they and their relatives need. Not even the richest individuals can “buy” efficient, safe drugs developed for their own needs.

Staying on the current path, governments will be faced with escalating healthcare costs in the face of declining economies.