THE DEVELOPMENT CHALLENGES
The best place to start the story of Tamiflu is undoubtedly at the very beginning of its life—with its birth. Tamiflu was developed in the 1990s as part of a new class of antiviral medicines for influenza called neuraminidase inhibitors. I will explain how these medicines are intended to work shortly. The key thing to note for the time being is that Tamiflu was not actually the first such neuraminidase inhibitor to be developed. That distinction went to another drug called Relenza. Tamiflu is only the second because it was developed as a direct commercial rival to Relenza. In fact, the whole birth of Tamiflu is inextricably bound up with the development of Relenza immediately before it. This chapter therefore initially explores how Relenza was developed as the world’s first neuraminidase inhibitor to address the problem of flu—and out of the direct shadow of which Tamiflu would soon be born.

Revisiting this story of Relenza reveals that pharmaceutical companies developed neuraminidase inhibitors through a fairly conventional process of commercial drug development. That conventional process usually consists of private-sector companies marrying a scientific discovery to an intense process of commercial development, taking the innovative discovery from the “bench” to the “bedside.” In the case of neuraminidase inhibitors, the decoding of the precise molecular structure of one of the influenza virus’s key surface proteins allowed a new drug target to be identified. Based on that scientific understanding, it was then possible to design and synthesize an artificial new molecule that could interfere with the processes of viral replication taking place inside the human body, and that could form the basis for a new pharmaceutical intervention. Scientific advances in
molecular biology had effectively opened up new avenues of commercial exploitation for pharmaceutical companies.

In addition to such scientific advances, however, the conventional process of new drug development also relies heavily upon the existence of a commercial market that the medicine can then be sold to. That market is crucial for companies to be able to recoup the significant up-front investment costs that are usually involved. A major reason why this commercial drug development process worked successfully in the case of Relenza is that such a lucrative market did indeed exist in the case of flu. However, that commercial market was not *pandemic* flu; rather, it was the closely related problem of *seasonal* flu, which spurred on the initial development of neuraminidase inhibitors. Companies were primarily interested in the commercial potential of neuraminidase inhibitors to address the problem of seasonal flu affecting tens of millions of people around the world every year. Neuraminidase inhibitors, it turns out upon closer inspection, were born very much as *accidental* medical countermeasures. They are largely the fortuitous byproduct of fairly conventional commercial efforts to address the parallel problem of seasonal flu.

What is more, it actually seems rather unlikely that neuraminidase inhibitors would ever have been commercially developed without this sizable parallel market in seasonal flu and solely to address the threat of pandemic flu. Taken on its own, that pandemic flu market is simply too uncertain and too unpredictable to justify the costly up-front commercial investment that is required. Nobody knows for certain if and when such a pandemic will occur or indeed what exactly it would look like, even if it does. Herein also lies the main reason why this conventional model for commercial drug development usually does not work very well for medical countermeasures in general. When it comes to most other health security threats, such a parallel market that could drive the commercial drug development process forward simply does not exist in the same way that it does for flu, and flu marks much more of an exception than the general rule in this regard. Without the promise of such a lucrative commercial market, most pharmaceutical companies simply fail to detect sufficient commercial potential in the whole area of health security and tend to steer a wide birth around medical countermeasures when deciding which products to prioritize and develop. When it comes to medical countermeasures in general, the conventional political
economy of commercial pharmaceutical development thus becomes profoundly disrupted.

Some of the very earliest experiences with the birth of neuraminidase inhibitors thus already reveal two quite formidable—and also much more general—challenges that will confront any government wishing to acquire new medical countermeasures from the outset. First, there will be difficult scientific challenges that will need to be overcome before any new medical countermeasure can be successfully developed. Second, there will also be significant economic challenges, unless governments can find other ways to incentivize pharmaceutical companies to take on the commercial development costs associated with new medical countermeasures.

**The Pandemic Flu Threat**

Most people will have first encountered neuraminidase inhibitors like Relenza and Tamiflu in the context of pandemic flu. Perhaps they heard about them through the extensive media coverage they attracted during the international outbreaks of deadly human cases of H5N1 (“bird flu”) and H1N1 (“swine flu”) infection. Perhaps they read about then when, one by one, governments around the world rushed to build vast stockpiles of the drugs at a cost of billions of dollars. Or perhaps they even took the antiviral medicines during the 2009–2010 H1N1 pandemic, as millions of people around the world were urged to do by their governments. In either case, many people’s first encounter with neuraminidase inhibitors would have been as a medical countermeasure against pandemic flu.

What exactly is pandemic flu? A flu pandemic is simply an epidemic of a new influenza virus spreading on a worldwide scale and infecting a large proportion of the human population. Influenza viruses are constantly circulating and have many natural hosts. Besides human beings, influenza viruses can also infect pigs, ducks, chickens, ferrets, and even horses. In fact, the very existence of influenza viruses was first discovered in pigs (in 1931). Some 20 years later aquatic birds were then determined to be natural hosts of influenza viruses (Klenk 2012). That said, influenza viruses can and do cause infections in human beings, which tend to manifest themselves in the onset of respiratory disease.

From the perspective of human health, probably the most significant aspect of influenza viruses is their inherent genetic instability. Many other
viruses that cause human disease, such as measles, mumps, and smallpox, are genetically comparatively stable. Once people have been vaccinated and their bodies have developed antibodies, immunity can be quite long lasting. Influenza viruses, by contrast, have a comparatively high mutation rate and are constantly changing as they circulate (Klenk 2012). Influenza viruses are fast-moving targets in that sense.

There are two different ways in which new influenza viruses can emerge: through antigenic drift and antigenic shift. Antigenic drift is a more gradual process. It is usually behind the seasonal evolution of flu viruses that occurs from one year to the next. This process tends to be associated with minor changes in the structure of the viral proteins (Varghese et al. 1983: 35). Antigenic shift, by contrast, is a much more substantial and abrupt reassortment process. Entire gene segments can become replaced, potentially leading to increased human vulnerability to the resulting new virus (MacKellar 2007: 431). Such reassortment events can also occur in animals (such as pigs) that are susceptible to both human and avian influenza viruses and can thus serve as mixing vessels (MacKellar 2007: 431–432).

When such substantially novel influenza viruses are introduced into the human population, new pandemics can arise. That has happened on at least three separate occasions in the twentieth century alone. The Spanish flu of 1918–1919 killed more than an estimated 20 million people, with some estimates even putting the worldwide figure as high as 50 million (CDC 2005). Two subsequent but comparatively “lesser” flu pandemics of 1957 and 1968 killed an estimated one million people each (MacKellar 2007: 431). After further analysis of the 1918 (H1N1) virus, it is now thought that the 1918 pandemic was caused by an avian flu virus. The virus probably adapted to human beings without first passing through an intermediary animal host. The pandemics of 1957 (H2N2) and 1968 (H3N2), by contrast, were likely caused by a reassortment of genetic materials (shift). Historians have also identified older, globalized epidemics (pandemics) that occurred during the nineteenth century—such as the Russian flu of 1889–1893 (Laver and Garman 2002: 1309). Influenza pandemics have thus occurred repeatedly throughout history.

The episodic recurrence of such influenza pandemics leads many experts to believe that new flu pandemics occur roughly once every couple of decades. The exact timing and extent of future pandemics cannot be predicted with any degree of certainty. When they do occur, however, new influenza
Pandemics are often distinguished by comparatively higher “attack” rates—that is, the number of people experiencing clinical symptoms of infection. The viruses responsible for the 1918–1919 and 1957–1958 pandemics, for instance, had estimated attack rates of around 25 percent, compared to around 10 percent in a normal flu season in the United States (MacKellar 2007: 430–431). Such elevated attack rates can also generate a substantially higher burden of disease and mortality and may cause more widespread social and economic disruption.

There can be other significant differences between pandemic flu and seasonal flu. For instance, pandemic flu can occur at any time of year and can come in multiple waves. It can affect people of any age—rather than predominantly killing those who are either very old or very young. In addition to the direct mortality and morbidity associated with influenza pandemics, they also tend to produce much wider economic and social disruption. They can affect travel, trade, and critical infrastructure and can require the closure of schools and so forth. That is why the identification of lethal human infections with novel influenza viruses generates such international concern. There is always the specter that it might mark the beginning of the next human pandemic.

Precisely such concern also formed the backdrop against which public health officials raised alarm in 1997 over new human infections with a highly pathogenic strain of avian flu in Hong Kong (MMWR Weekly 1997). The H5N1 viruses were killing thousands of birds at the time, but they could also infect people coming into close contact with infected animals. It was the first known instance of human infection with this avian H5N1 virus (WHO 2011b). Although the officially reported number of human cases was still fairly low (18 in total), 6 of the cases proved fatal. That made the virus comparatively lethal. With the last influenza pandemic having occurred several decades earlier, experts became concerned that this could mark the beginning of a “long overdue” new human influenza pandemic. Control measures were quickly introduced in Hong Kong, and the initial outbreak was contained. Then things went quiet for several years.

In 2003, however, new human infections with the potentially deadly H5N1 virus suddenly reappeared, again in Hong Kong. This time the news was accompanied by reports of other human infections also occurring much more widely across other geographic areas in Southeast Asia and beyond. Tracking this alarming spread of H5N1, countries began to draw up much
more extensive pandemic preparedness plans. The World Health Organization warned that a new pandemic infecting roughly 25 percent of the world population (a figure derived from previous pandemics) could affect more than 1.5 billion people and cause enormous social disruption because of a rapid surge in illnesses and deaths (WHO 2007: 47). In the United States, the CDC also warned that in the absence of any control measures (vaccination or drugs) a “medium-level” pandemic would cause 89,000 to 207,000 deaths, 314,000 to 734,000 hospitalizations, 18 million to 42 million outpatient visits, and another 20 million to 47 million people being sick in the United States alone. It further warned of economic consequences: “Between 15% and 35% of the population could be affected by an influenza pandemic, and the economic impact could range between $71.3 and $166.5 billion” (CDC 2005).

Confronted with the specter of such scenarios, many governments began to prepare in earnest for the arrival of a potentially catastrophic new human flu pandemic. The pandemic flu threat rapidly rose to the top of government agendas and was even added as a new threat to the national security strategies of several countries. High-level simulation exercises were carried out to test cross-government levels of preparedness. New government strategies on pandemic flu were set out. Wide-ranging international diplomatic initiatives on pandemic flu were also launched, and the threat was extensively discussed at a high level in a plethora of regional and international organizations. Pandemic preparedness became a new political buzzword on many people’s minds. If it did materialize, such a flu pandemic would represent precisely the kind of global health security threat against which governments would like to better protect their populations in the twenty-first century.

**How to Respond? Preparing for the Next Pandemic**

What could governments actually do to strengthen the protection of their populations against this threat lurking at their door? If the lethal H5N1 virus evolved further and become readily transmissible between human beings, governments around the world would have a serious challenge on their hands. One option, of course, would then be to resort to more traditional public health interventions. There are many of these to choose from—like emphasizing personal hygiene, dispensing face masks, setting up quarantines, introducing travel restrictions, restricting mass gather-
ings, and so forth. Plans for introducing several of these measures were considered by governments, and additional evidence on their likely effectiveness was also gathered. But in the event of a highly transmissible virus, would such actions really be able to stop a burgeoning pandemic in its tracks? Or would they at best delay it for a short while? With so many urban places characterized by high population density, with so many different flows of livestock and people involved in international trade, it would likely prove very difficult to contain an outbreak in all but the best-case scenarios. No doubt it would be safer—and more reassuring—for governments to also have a medicine or vaccine readily at hand to protect their populations.

Surely such a safe and effective pharmaceutical intervention exists for flu that governments could easily deploy for the purposes of their pandemic preparedness planning. After all, there have been so many advances in medicine and pharmacology during the course of the past century alone. It is certainly true that many new medicines were developed in the twentieth century. Since the late 1920s, for instance, doctors have gradually seen the development and introduction of more than 80 different antibiotics to treat a range of bacterial infections. When it comes to influenza, however, the therapeutic landscape is markedly different, and there are actually far fewer medical options available than people might think.

One reason for this is that viruses, not bacteria, cause influenza. Viruses tend to be physically much smaller than bacteria. They also replicate inside human cells. That makes them much more difficult to target pharmaceutically, especially without also destroying their human host cells in the process. In fact, the very first antiviral medication (as opposed to antibiotic therapy) only became available in the 1960s, and over the next 25 years only four additional ones were developed (Dolan and Moukheibe 2003). Not until the AIDS pandemic would the pharmaceutical landscape of antivirals become radically transformed, which then stimulated the development of 23 new drugs in a space of just 15 years (Dolan and Moukheibe 2003). Developing safe and effective antiviral medications for flu thus remains very challenging, even today.

Why is it so challenging? A big part of the challenge has to do with how the human body responds to influenza viruses. The immune system normally “defends” itself against new microorganisms by producing specialized cells that destroy these tiny microbial attackers. The downside of this
mechanism is that it takes some time for the process to unfold. In the meantime, the infection could already have progressed far enough to cause a range of unpleasant symptoms. But there is also an upside. Once this process has run its course, the body will generally be well protected against any future “invasion” of that same virus. This is because the next time around it will be able to produce the correct antibodies much more rapidly. That is also the reason why people usually only get diseases like measles once and are protected thereafter. On top of that, there are ways for people to get ahead of the curve by using preventive vaccines, which can stimulate the body into producing relevant antibodies in advance of an infection. Once a new virus enters the body, the immune system will then recognize the pathogen and can fight off the infection before it causes much harm.

When it comes to influenza, however, things are not quite as straightforward. Because influenza viruses are constantly mutating, the surface of the virus can look different from one year to the next (Schneider 2001). This means the immune system does not recognize and cannot efficiently fight off the new infection. The result is that the process of influenza infection can start all over again, leading to the recurrent problem of seasonal flu affecting so many people around the world year after year. From the perspective of the human immune system, the flu virus is a constantly shifting target, and so the system struggles more. It is simply a more complex challenge.

That very same problem also makes the use of medical interventions much more difficult in the case of flu. As we have just seen, vaccines usually work through the advance stimulation of the human immune system (prompting it to create new antibodies). This means vaccines usually have to be virus-specific in order to be effective. However, as the flu viruses keep changing from season to season, it is possible for the circulating influenza viruses to differ significantly from those included in the widely used flu vaccines. In that case, the latter will not offer much protection. With influenza forming such a constantly changing and fast-moving target, it is hard to predict exactly which of the many circulating strains will come to dominate during the next flu season. On top of this, there is also the problem that vaccine manufacturers still need a considerable lead time (spanning many months) to mass-produce seasonal flu vaccines.

At the moment, then, the best that influenza experts can do is to take a highly educated guess as to which strand of flu virus might be circulating
in the next flu season. That is precisely what they do twice a year—once for the Northern Hemisphere, and once for the Southern Hemisphere. The processes of choosing the “right” viruses for the next vaccines are a finely tuned mix of science and art. Working with these recommendations, industry then begins the process of mass-producing the vaccine to ensure that the supplies are available in time for the flu season. Depending on how good the match turns out to be in the end, the process of seasonal flu vaccination is more successful in some years than in others. In any case, however, it is a process that must be repeated every year. It’s a cumbersome and costly method, and many people of course also prefer not to be vaccinated. The ever-changing nature of influenza viruses thus complicates the use of medical interventions to manage the challenge they pose.

All of these issues are only exacerbated in the case of pandemic flu. It is, by definition, not possible to know in advance exactly what form a new pandemic influenza virus might take, making it is extremely difficult to develop an effective preventative vaccine prior to any flu pandemic occurring. That uncertainty alone creates a huge obstacle for a vaccine-based strategy for protecting populations against pandemic flu—though some prepanemic vaccines have recently been developed. How can an advance vaccine be developed against a flu virus when it is not known exactly what such a pandemic virus will look like?

Why, then, can governments not simply wait for a new pandemic flu virus to emerge and then quickly mass-produce a new vaccine based on that exact virus? Here the catch is, once again, the long lead time it takes time to mass-produce a vaccine. In the current model of vaccine production, it takes at least six to nine months to mass-produce a new pandemic vaccine, and that assumes that the process goes smoothly. Flu vaccines are traditionally also grown in eggs, and there may not be sufficient eggs available to meet pandemic demand for vaccine. So it would be several months, perhaps even a year, before a steady supply of pandemic flu vaccines specifically matched to the new strain would become available. In the meantime, countries would have to endure the full-blown effects of a pandemic for many months, without the availability of a protective vaccine for their populations.

There is also another catch. The scenario described above pertains to countries that possess their own vaccine manufacturing base. Most countries around the world, however, do not even possess their own domestic
vaccine production capabilities. Once a pandemic vaccine does finally become available, there will not be nearly enough supply to meet global demand. That in turn raises nightmarish humanitarian scenarios around unequal global access to vaccines and around who in the world will be left unprotected from a lethal virus. There are thus several significant problems with relying on vaccines to protect populations against the threat of pandemic flu, ranging from their underlying mechanism of action to the technical challenges of developing new vaccines, as well as the limits of the current international political economy of vaccine production.

When it comes to pandemic influenza, then, governments are actually left confronting a quite unsavory and thorny political scenario. In the event of a new flu pandemic, they would initially have to let the virus run its course for many months while they wait for a virus-specific vaccine to gradually become available—provided, that is, they even have production capacity or are at least able to secure orders from elsewhere. This long period of delay could have devastating social, economic, political, and public health ramifications. During this period, governments would also run the political risk of being seen as weak, even negligent, in their core duty to protect the welfare of their populations. All the while, the virus could wreak immense human and socioeconomic havoc. It is clearly not a very desirable scenario for governments or indeed their people.

Are there not any other pharmaceutical interventions besides vaccines that governments could possibly opt for instead? The only other pharmaceutical option to protect populations against flu are antiviral medications. They differ from vaccines in that they do not work by priming the human immune system against a specific virus in advance of infection. Instead, antiviral medications seek to interrupt the process of viral replication taking place inside the human body, thereby buying valuable time for the human immune system to do its work. Antivirals thus offer the prospect of a very different approach from the vaccine-based strategies.

The problem with antivirals, however, is that there simply are not many types of influenza antivirals on the market. Notable examples from the past include amantadine and rimantadine. Developed in the 1960s, they represented the first class of influenza antivirals. They may superficially appear to be a more appealing option when compared to vaccines. One particularly attractive feature, for instance, is that they could work across a wide range
of influenza viruses—unlike vaccines, which need to be virus-specific. In practice, however, these early influenza antivirals proved only modestly effective from a clinical point of view. They were also associated with several side effects, and viruses tended to become resistant to them very rapidly (Schneider 2001; von Itzstein 2007: 967). There would thus be significant issues with governments relying upon their widespread use during a pandemic.

The bottom line with regard to pharmaceutical interventions for pandemic flu is therefore actually this: all the medical advances of the twentieth century notwithstanding, the best that most people could immediately hope for in terms of medical interventions would be symptom-relief medication. A wide range of such over-the-counter products is already on offer in many countries. These may make people feel better by relieving some of the unpleasant symptoms of flu, but they do not combat the underlying virus infection. Upon reflection, it is not a particularly impressive or reassuring state of affairs—not for individual patients, and not for governments wishing to protect their populations against a future flu pandemic that many experts expect will eventually occur.

In the absence of such pharmaceutical interventions, the only other option is for governments to fall back upon their more traditional public health measures. These essentially seek to reduce the human spread of the virus by curtailing the movement of people. They can entail a variety of measures—like school closures, canceling public events, quarantine, isolation, temperature screening at airports, and so forth. Yet these measures, too, clearly have a number of drawbacks. Their introduction does not tend to be very popular politically, as they entail infringing upon the free movement of citizens. There are also questions about how effective they would be in practice. And they would of course result in the shutting down of many systems of circulation that are vital to the overall welfare of the population, such as trade, travel, education, and so forth. These measures may end up saving lives, but from an economic and social point of view, the interventions would be nearly as bad as the pandemic itself. In this scenario, too, there would be immense socioeconomic disruption. The “cure,” in short, would not be that much better than the “poison.” When it comes to confronting the specter of pandemic flu, there are simply very few attractive policy options for any government wishing to effectively protect its population.
A New Molecular Dawn: The Scientific Birth of Neuraminidase Inhibitors

The limited therapeutic landscape for flu would only begin to change in the late 1990s with the development of a second generation of antiviral medications called neuraminidase inhibitors. A much-improved scientific understanding of the molecular processes involved in viral replication had made their development possible. After the first human influenza virus was isolated in 1933, scientists began to understand that viruses cannot replicate on their own. To do so, they first have to insert themselves into other cells. They can then “hijack” those cells in order to make more copies of themselves. The newly formed virus particles subsequently leave the host cell again, destroying the cell in the process. Once released, the newly formed viruses can then also go on to infect further cells, repeating this cycle over and over again and causing disease in the human body (Schneider 2001).

Over the course of the twentieth century, scientists gradually refined their knowledge of all of these molecular processes unfolding inside the human body during an influenza infection. One such scientist was George Hirst, who is widely regarded today as a historic pioneer in molecular virology. Working at the famous Rockefeller Institute in New York in the 1940s, Hirst suspected that influenza viruses possess a crucial enzyme that destroys virus receptors on host cells (Laver et al. 2000: 180). It was a critical hypothesis, as it was later confirmed that such an enzyme—called neuraminidase—does indeed exist. As the newly formed viruses leave the host cell, they become attached to a sticky coating of sialic acid found on the surface of the host cell. In order to unstick themselves they therefore have to rely on the work of this critical enzyme called neuraminidase. Metaphorically, the neuraminidase acts like a pair of scissors that cuts newly formed virus particles free from the surface of their host cells, allowing these new virus particles to then go on to infect yet more cells, thus extending into a wider infection. Without necessarily knowing it, many will already be familiar with this neuraminidase because it is widely identified by the “N” designation in the international virus classifications commonly used in the scientific literature and also frequently reported in the media for naming influenza viruses—like H5N1, H1N1, H7N9, etc. (where the H refers to the other surface protein called hemagglutinin, which allows viruses to stick to the surface of cells lining the respiratory tract).
All of this begs the question of what would happen to influenza viruses without the proper functioning of this critical neuraminidase? In that case, the new viruses would not be destroyed, but they would likely remain stuck on the surface of the host cell, unable to free themselves. Being stuck, they could not easily go on to infect other cells, as would be necessary for causing a wider and more severe infection in the body. Therefore, if there could be a pharmaceutical way to disrupt or inhibit the proper functioning of this crucial neuraminidase enzyme, that could mark an exciting entry point for a new type of antiviral medication—at least in theory.

That highly attractive prospect moved a big step closer in the 1970s and 1980s, when the precise molecular structure of the neuraminidase enzyme was first decoded. The Australian scientist Professor Graeme Laver had found a way of spinning neuraminidase into a crystalline form (using a centrifuge). Laver was working for the Australian National University in Canberra at the time. By his own admission, creating such a crystalline form of neuraminidase was largely a matter of serendipity. In an email to one of his students he later recalled how the idea of trying to crystallize neuraminidase came to him in March 1977, while he was on a long flight from Europe back to Australia. He was adamant that his discovery was essentially one of “sheer luck and not at all intentional” (Laver n.d.). In fact, initially Laver did not really know what he should do with the new crystals. He did not realize at the time that having the neuraminidase in such a crystal form, rather than in its normal amorphous form, would soon open up critical new possibilities for studying it scientifically (Jack 2006).

Laver was later introduced to Peter Colman, who was working in Melbourne at the protein chemistry division of the Australian research organization called the Commonwealth Scientific and Industrial Research Organization (CSIRO). A number of scientists at the time were beginning to map the precise chemical structures of biological molecules through a new technique called X-ray crystallography. For the process to work properly, however, scientists first needed a crystal of the molecules they wished to study. That crystal would then be placed in a beam of X-rays. Analysis of the resulting diffraction patterns would allow the relative positions of the atoms and molecules to be determined. Having the neuraminidase enzyme in its crystallized form (thanks to Laver), Colman could now use that very same technique to also “solve” the neuraminidase enzyme’s crystal structure. He did so and then published the findings in *Nature* in 1983.
(Varghese et al. 1983). By 1983 scientists were thus able—for the first time in history—to map the spatial arrangement of the thousands of atoms that make up the neuraminidase molecule.

Decoding these precise molecular structures yielded yet another critical discovery, perhaps the most pivotal one of all. The surface of influenza neuraminidase can change from one influenza virus to another. Yet the scientists also managed to find a crucial site that appeared to remain constant across most influenza viruses, a deep cleft or pocket-like cavity. This may sound like a lot of scientific detail, but this static site could effectively turn out to be the influenza viruses’ Achilles heel. If this site remained very stable, even as influenza viruses constantly changed, it could be a valuable site that a new type of drug could target (Schneider 2001; Webster 2010: 230). With this new knowledge about its precise molecular structure, it might now be possible to engage in a project of rational drug design by deliberately designing a new synthetic molecule to work upon this newly identified target (Laver and Garman 2002: 1312). The refined scientific understanding of the molecular structure and processes involved in influenza infection had suddenly opened up the possibility of a new therapeutic approach.

To take this project forward, Laver and his colleagues next set up a new biotechnology company in Australia called Biota Holdings. CSIRO and the university did not have the funds to support the commercial development of the new drug target. So Biota Holdings purchased the patents and then sought funds to develop the drug at the Victoria College of Pharmacy in collaboration with Mark von Itzstein (O’Neill 1989). A team of researchers led by von Itzstein studied the crucial cleft and then used computer simulations to design a new molecule that would “plug in” to it (Jack 2006). In essence, that is how the world’s first neuraminidase inhibitor was born. Von Itzstein published the exciting discovery in the prestigious scientific journal *Nature* in 1993. It promised to be a major breakthrough.

To be clear, even if it worked as intended, this new molecule would not actually “cure” people of the flu. It would not even destroy the viruses already inside the human body. But the idea was that it could help to suppress the process of viral replication in the human body. In theory, that would buy valuable time for the natural immune system to respond to the (reduced) infection, provided the therapy was started in the early stages of infection. It promised to be a major advance in the therapeutic landscape for
influenza. Laver had made the crystals; Colman had solved the molecular structure and discovered the site; von Itzstein had made the new drug. All three therefore shared the 1996 Australia Prize for their contributions to this critical development. On paper at least, neuraminidase inhibitors heralded the prospect of doing something that human evolution could not—finding a way of keeping the influenza virus in check. A series of scientific breakthroughs now heralded the prospect of a very new way of protecting people against the flu.

Nor is it hard to see the potential attraction of this new antiviral from the perspective of governments also trying to better protect their populations against the threat of pandemic flu. A whole new way of managing the influenza threat pharmaceutically had suddenly become possible. Crucially, these new antivirals would not have to be virus-specific in the same way that vaccines had to be. Because the scientists had identified a static site, there was a good chance that neuraminidase inhibitors would work across a broad cross section of influenza viruses, including future ones that might cause a pandemic. This meant that neuraminidase inhibitors could probably be administered almost immediately after the outbreak of a new influenza pandemic, in contrast to the long lead time of many months needed for new pandemic vaccines to become available. Provided such antivirals were readily at hand in sufficient quantities, neuraminidase inhibitors could effectively form a new first line of defense against pandemic flu and could buy governments valuable time until pandemic vaccines became more widely available. Neuraminidase could finally give government planners the option of responding to an anticipated flu pandemic pharmaceutically, without first having to wait many months and without resorting to much more intrusive public health measures. Before any of these potential benefits could accrue, however, there was still a lot of commercial drug development work that would need to be carried out first.

From Bench to Bedside: The Commercial Lure of the Seasonal Flu Market

No matter how ingenious the scientific discovery, taking a promising new drug candidate from the “bench” to the “beside” is a complicated and costly process. It involves carrying out large-scale clinical trials, gaining regulatory approval, building commercial production facilities, developing marketing strategies, and so forth. Somebody has to have the expertise to
carry out these tasks as well as the funds to take on the considerable commercial risk involved. Clearly that company could not be Biota. As a new and small biotechnology company, it had neither the skills nor the funds nor the experience to do all of these things on its own. In order to move the new molecule forward to the next stage of its commercial development, the company would need the help of a much larger and more experienced pharmaceutical company.

Fortunately, Biota found one such company that was interested, and in 1990 Biota licensed the new compound to the UK-based pharmaceutical company Glaxo Wellcome. As a large and well-established pharmaceutical company, Glaxo Wellcome possessed the requisite funds and expertise in drug commercialization that Biota lacked. In an interview about the new neuraminidase inhibitor with the Australian Broadcasting Corporation in 1999, Laver recalled just how crucial it had been to find that partner: “You wouldn’t believe the number of knock-backs we had and it only took off when one of the big drug companies took it up and then all the other big drug companies wanted to be in it too” (Laver 1999). Asked whether he was surprised that the compound was licensed to a UK-based rather than an Australian company, Laver tellingly replied: “Surprise? . . . No, because we know it’s effective and we know that there’s a huge market for it and to develop these drugs, taking them from the lab to the clinical trials to the community literally costs hundreds of millions of dollars. And, no. I mean, there’s no company in Australia big enough for it” (Laver 1999).

With the benefit of hindsight, then, it is clear that Glaxo Wellcome’s decision to take on the new drug candidate was absolutely critical for transforming it into a product that could eventually be prescribed to patients and stockpiled by governments against the threat of pandemic flu. Biota would not have been able to undertake this work on its own. Without a partner like Glaxo Wellcome, the new drug candidate would likely have simply lingered on or fizzled out with no one willing to take it forward. It would have gone down in history as a laudable scientific discovery but not much more than that. With a single stroke, Glaxo Wellcome’s decision seemed to change all of that.

So why did Glaxo Wellcome decide to take on this new product? The company decided to do so mostly on quite conventional commercial grounds. In fact, its decision at the time appears to have had very little if anything to
do with health security considerations about pandemic flu. Instead, the company was mostly interested in the lucrative market for seasonal flu. Why seasonal flu? To the casual observer seasonal flu may not seem like a particularly significant public health problem, especially when compared to the more menacing specter of pandemic flu. It might not appear worthy of sustained interest by pharmaceutical companies seeking to generate high-revenue producing “blockbuster” drugs. The symptoms of flu are unpleasant, to be sure; they include fever, cough, sore throat, myalgia and headache. Yet for adults who are otherwise healthy, seasonal flu is usually also a self-limiting illness. When left untreated, it tends to run its course in a matter of one to two weeks. One could therefore be forgiven for wondering why any large pharmaceutical company would want to invest immense sums of money into developing a new treatment for seasonal flu. That is especially true when one also considers the fact that there are already so many over-the-counter products readily available for relieving or reducing many of the flu’s unpleasant symptoms.

In reality, however, the seasonal flu landscape is a little more complicated than this simplistic picture suggests. Even when flu is not life threatening, the symptoms are sufficiently unpleasant that many people might be willing to pay significant sums of money each year on a wide range of symptom-relief medications. That market would represent a sizable commercial opportunity for any company that could develop an effective, safe, and easy-to-take pharmaceutical “fix.” At the time that companies were developing neuraminidase inhibitors, estimates indicated that each year there were around 100 million people suffering from seasonal flu in the world’s major pharmaceutical markets such as the United States, Japan, and Europe (Schneider 2001). For those with sufficient disposable income, a new flu treatment could be marketed as a way for preventing the onset of the unpleasant symptoms of flu. That was a potentially hugely attractive commercial market.

The large number of people who are affected by flu every year could also provide a new drug with an additional public health market. The sheer volume and scale of annual influenza infections generates a substantial public health and economic burden in many societies around the world. The CDC, which is charged with protecting public health and controlling disease in the United States, estimates that every year—on average—between 5 and
20 percent of the population becomes infected with the flu in the United States, leading to more than 200,000 annual hospitalizations linked to flu-related complications (CDC 2012). A potential new influenza therapy might thus also be considered by governments as part of their wider public health strategies. It is, after all, precisely because of this burden that many governments already make seasonal flu shots available for many people. Here a new antiviral treatment held out the prospect of also tapping into a significant public health market, broadening the commercial opportunities further still.

Finally, it is important to bear in mind that there are also circumstances in which an influenza infection can kill—especially in persons with a number of other underlying medical risk factors. Those at risk from flu complications include groups like older people, young children, pregnant women, and people with certain underlying health conditions. Between 1976 and 2006, annual estimates of flu-related deaths range from 3,000 to 49,000, depending on the severity of the flu season (CDC 2012). There was thus a reasonable prospect that a new antiviral might also be used preventatively in places like nursing homes for the elderly. That, in turn, could represent yet another commercial market.

When one considers all of these possibilities, then, there is actually a potentially very sizable, lucrative, and recurring commercial market of people and institutions that might be willing to pay for a new influenza treatment. This predictable and potentially highly profitable commercial market for a common illness affecting millions of people a year—every year—is what ultimately prompted a large pharmaceutical company like Glaxo Wellcome to enter the proverbial “ring” and invest its extensive resources and expertise in taking Biota’s new molecule forward. So the molecular discovery was further developed and eventually turned into a new pharmaceutical product that could obtain regulatory approval and be prescribed to patients. The name they gave this new product in the end was Relenza, which reportedly derives its trademark name from RELief of influenza (Garfield 2009). All of this also means, however, that the major driver for the commercial development of the world’s first neuraminidase inhibitors was seasonal flu, not pandemic flu. Upon closer inspection it turns out that neuraminidase inhibitors were very much born as accidental medical countermeasures; they are largely the fortuitous byproduct of fairly conventional commercial efforts to address the parallel problem of seasonal flu.
Where Is the Market for Medical Countermeasures?

The fact that the world’s first neuraminidase inhibitor was largely developed with seasonal flu in mind—and not for pandemic flu—is highly significant for the wider quest to develop new medical countermeasures. It suggests that pharmaceutical development tends to be driven by strict commercial logics and not by security considerations. Governments may well be keen to acquire new medical countermeasures to better protect their populations and economies against an array of biological threats like pandemic flu. Most pharmaceutical development, however, is carried out by large pharmaceutical companies that are driven by commercial considerations and market forces. Indeed, we have just seen that the main reason why a large pharmaceutical company took a neuraminidase inhibitor like Relenza forward was because of the sizable commercial market for seasonal flu. To put that point another way, the fact that we have at least some medical countermeasures against pandemic flu available today (in the form of neuraminidase inhibitors) is largely due to an accident of history. It is essentially explained by the Janus-faced nature of flu.

If that is true, however, it immediately begs another question: What would have happened to this exciting new molecule without the existence of that parallel commercial market for seasonal flu? Would a large pharmaceutical company like Glaxo Wellcome still have taken on its risky commercial development solely on the basis of the pandemic flu threat? It is impossible to be certain about such a counterfactual scenario, but it does seem rather unlikely. The threat of pandemic flu on its own would probably have proved too unpredictable and diffuse to justify the level of commercial investment needed. As Angus Nicoll put it at the time in his capacity as the head of the influenza program at the European Centre for Disease Prevention and Control (ECDC), when it comes to pandemic flu we just “don’t know when one is going to happen, where it will start or what it will be like” (Nicoll and Sprenger 2011: 191). There is just too much uncertainty around the threat of pandemic flu in terms of when (or indeed if) it will arise, how large it will be, and exactly what it will look like. It is very difficult to construct a persuasive commercial business model around such a high degree of uncertainty.

That same fundamental uncertainty also plagues most other health security threats. Consider, for example, the threat of bioterrorism. It too remains highly unpredictable and deeply uncertain. Will such an attack ever
occur? What agent would be used? How many people would likely be affected? Where would it occur? All of that uncertainty again makes it very difficult to construct a viable business case for developing a costly new medical countermeasure. How can a large commercial pharmaceutical company, existing in a competitive environment and with shareholders to satisfy, construct a commercial business case for developing a new drug against a threat for which it is not known when it will materialize, if it will materialize, and—even if it does materialize—who and how many people it will affect? Overall, the cost of new medical countermeasure development simply remains too high compared to the low frequency and massive uncertainty around health security threats. In many ways, the market for medical countermeasures is the exact opposite of what most commercially operating pharmaceutical companies would be looking for in an attractive business case to take a new product forward.

Moving from the development of more routine pharmaceuticals to the world of security and medical countermeasures thus alters the overall commercial equation for new drug development considerably. The conventional political economy of pharmaceutical development that worked so well—but essentially accidently—in the case of flu, is unlikely to work when applied to most other health security threats. Unlike flu, these other biological threats simply do not have a parallel commercial market to drive the costly drug development process forward. When it comes to the world of medical countermeasures more generally, the conventional political economy of pharmaceutical development is therefore profoundly disrupted, and it remains unclear who will take the development of such products forward, especially given the fact that almost all drug development nowadays is carried out by large commercial pharmaceutical companies.

Instead, a considerable gap begins to open up between the growing political demand for new pharmaceutical defenses expressed by governments on the one hand and the lack of commercial drivers that pharmaceutical companies are looking for in order to develop such products on the other. Precisely that gap also helps to explain why, in practice, it has actually proved very difficult for governments to persuade (especially large) pharmaceutical companies to become more actively involved in the quest to develop new medical countermeasures. The increased political desire for developing novel medical countermeasures is simply not very well aligned with the research and development priorities of large pharmaceutical com-
panies, most of which avoid the area of medical countermeasures. In the end, governments are thus left confronting a quite protracted economic challenge about how to persuade commercially operating pharmaceutical companies to develop new medical countermeasures in the absence of an underlying commercial market to sell those products into.

Revisiting these very earliest stages in the life of neuraminidase inhibitors, then, already reveals two major challenges confronting efforts to develop new medical countermeasures more generally—perhaps the two most formidable of all. The first is scientific. As with many new types of medicines, there are considerable scientific challenges that must be overcome before a new medical countermeasure can actually be designed. In the case of flu, our increased scientific understanding of the molecular processes involved in influenza virus replication revealed the way in which the surface proteins of the virus can mutate, possibly leading to new pandemic threats in the future. The subsequent decoding of the exact molecular structures of some of those surface proteins (especially neuraminidase) then led to the identification of a new drug target and eventually even the scientific design of an artificial new molecule to interfere with the process of viral replication. Even at that stage, however, the development of Relenza still experienced a number of setbacks along the way, and serendipity also played a pivotal role in its discovery. The task of developing new drugs is scientifically and technologically so complex that many promising drug candidates never see the light of day. John Rex, vice president and medical director for infection at AstraZeneca, put its plainly: “Most new or in-development pharmaceutical products fail” (quoted in Wizemann et al. 2010: 18).

There are several different points along the way where a promising new drug candidate can suddenly transform into a “no-go.” The three most significant factors impeding successful drug development are usually a failure in efficacy (the drug ends up not working as intended), a failure in safety (accounting for about two-thirds of failures), and failure in commercial considerations (e.g., cost to bring the product to market, perceived profitability of the product) (Wizemann et al. 2010: 5). The scientific challenges involved in new drug development cannot therefore be underestimated. Indeed, two industry experts explain: “We have so few drugs to show for so long and such expensive research not because we don’t try hard enough, not because we are ‘idiots,’ but because it’s extraordinarily hard to find effective,
safe new drugs” (Bartfai and Lees 2006: 15). Expectations about the future development of new medical countermeasures will need to be tailored to that underlying reality. Their scientific development will likely be a slow and at times painstaking enterprise, with a number of setbacks along the way to be expected. It also means that the option of generating a novel countermeasure quickly in response to an unfolding crisis still remains remote in many areas at present (Cole 2013: 27).

That said, all of this does also point to at least one longer-term strategy that governments could adopt in relation to medical countermeasures: investing in scientific research. Molecular biology played a key role for the discovery of neuraminidase inhibitors—by refining our understanding of the molecular processes involved viral replication, by decoding the precise molecular structures of key elements of the virus, and also by identifying new molecular targets that could form new sites of pharmaceutical intervention. Extrapolating from that experience, public investment in science could also lead to other fundamental discoveries in the future that could then form the promising basis for new medicines and vaccines, albeit perhaps not in a very linear manner or along the path originally anticipated. Supporting basic science would thus mark one potentially quite significant way in which government can still influence the process of medical countermeasure development over the long run.

In addition to these scientific challenges, however, governments wishing to encourage the development of new medical countermeasures will also confront a second, economic obstacle. New drug development is usually a commercial process profoundly shaped by market forces and logics. It is also a very risky and expensive one. Conventional commercial drug development thus tends to be driven by private companies lured by the promise of a sizable, recurrent, and predictable market to offset these costs and risks. That is exactly what happened in case of Relenza. A large and experienced pharmaceutical company decided to invest in bringing the product to market largely because of the lucrative commercial market for seasonal flu. So the conventional political economy of pharmaceutical development worked successfully in that case, in the sense that Relenza was eventually brought to market.

Beyond flu, however, such parallel commercial markets do not exist for most other health security threats, making it much more difficult for companies to compile a viable business case justifying commercial investment
in medical countermeasures. In the case of more widespread diseases, such as diabetes or cancer, a pharmaceutical company can usually calculate (or at least reasonably estimate) levels of demand, the price they can charge for their new product, the cost of development, the degree of market competition, and so forth (Matheny et al. 2007: 229). For health security threats, by contrast, no company can be sure when—or even if—a particular threat will materialize, how large the threat might be, and whether the threat is likely to repeat itself. Once a new product is developed, moreover, there will likely only be a handful of government buyers, perhaps even as few as one. The fact that medical countermeasures are aimed at rarer and more unpredictable security threats thus complicates matters considerably and begins to alter the underlying commercial equation for pharmaceutical companies. For most medical countermeasures, the conventional political economy of new drug development quickly falters because there is no parallel commercial market that companies can sell into. Most large pharmaceutical companies will simply steer a wide birth around the whole area of health security as a result. From the very outset, then, developing new medical countermeasures to protect populations involves confronting a formidable mixture of both scientific and economic challenges.