Chapter 4
The FDA

We Need Them, but They Have Become Part of the Problem

It is clear that we need a viable, strong, active and even interventionist FDA. But we also need new antibiotics. How did we get to a place where these two obvious needs might be in conflict?

The Food and Drug Administration had its origins in tainted food and agricultural products, contaminated antisera and bogus medicines sold to the public and to the US armed forces in the nineteenth century. The Bureau of Chemistry in the Department of Agriculture hired a chemist, Harvey Washington Wiley, in 1883. He worked to bring adulterated food products to public attention and then to study the effects of the adulterants in human subjects using his "poison squad" of volunteers. These revelations led in large part to the passage of the Food and Drugs act of 1906 – it was called the Wiley Act at the time. The law was mainly directed at appropriate labeling and making sure that additives and compounds were adequately pure and well described. The Bureau of Chemistry was charged with its enforcement.

After the election of FDR in 1932, it was becoming painfully clear to the public and to government that the 1906 law needed updating. With only labeling of ingredients as its mandate, the agency could not remove toxic or ineffective products from the marketplace. Several scandals brought this major shortcoming to public attention. An eyelash enhancer was causing severe reactions and even blindness. A worthless "cure" for diabetes was being sold. Finally, Elixir sulfanilamide was promoted for use in children. It had the sulfa antibiotic all right, but it was dissolved in a sweet tasting antifreeze derivative that killed 100 people, many of them children. The Food, Drug and Cosmetic Act of 1938 addressed these issues by requiring that drugs be approved before marketing. The agency was given powers to enforce prohibition of false claims and tolerance limits for certain noxious substances were mandated. Prescriptions were required for many drugs, including the new sulfa antibiotics.

The Pencillin Amendment was passed in 1945 in response to a large number of penicillin analogues being introduced to the market. The law required testing of safety and efficacy of all penicillin analogs, and ultimately all other antibiotics. The amendment was rescinded in 1983 as it was then considered superfluous.

D.M. Shlaes, *Antibiotics*, DOI 10.1007/978-90-481-9057-7_4,

As a result of the thalidomide tragedy, where the drug was used for the treatment of nausea in pregnancy and resulted in untold numbers of birth defects, the Kefauver-Harris Amendment was passed in 1962. It required drug manufacturers to prove efficacy as well as safety during pregnancy. This law greatly expanded the powers of the FDA.

A timeline of key events in the history of the FDA focusing on antibiotics is shown below (Fig. 4.1).

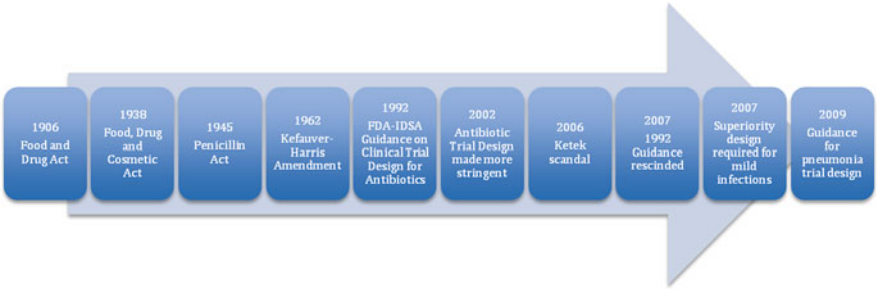

Fig. 4.1 A timeline of key developments at the FDA emphasizing those affecting antibiotics

I don't think that anyone can question the necessity of the FDA and the enormous good it has done for patients and physicians since it's founding. For antibiotics, though, things are starting to unravel.

Sulfonamides and penicillin were tested in clinical trials on only a few hundred patients with a variety of infections and were used topically, orally and intravenously. In some trials, untreated patients with similar infections seen at the same time as treated patients served as controls. In other trials, the only controls were untreated patients seen in the past with similar infections and where the same sorts of data were collected. Such patients would be historical controls. Although the FDA still accepts historical controls for some trials, especially in rare diseases or where the historical database is exceptionally large and robust, they are almost never used anymore to study antibiotics – and rightly so. We were so lucky. The marketed compounds went on to be used in the treatment of untold millions of patients over the years. No one doubts the utility and importance of these early antibacterial compounds for human use (except, perhaps, the FDA itself).

These days, drugs are withdrawn for serious side effects occurring at rates of 1 in 100,000 treated patients. Our clinical trials for antibiotics require us to treat just a few thousand patients before the drug is approved. Therefore, there is no way we would be able to detect rare but potentially serious side effects. Imagine what kind of a chance we were taking when drugs were approved after use in only a few hundred patients.

During the golden age of antibiotics between 1955 and 1985, as described in Chapter 6, Industry, FDA and the Infectious Diseases Society worked closely together to define how trials should be designed and evaluated. Recently, things have gone less well. The figure below shows approval of new antibiotics between

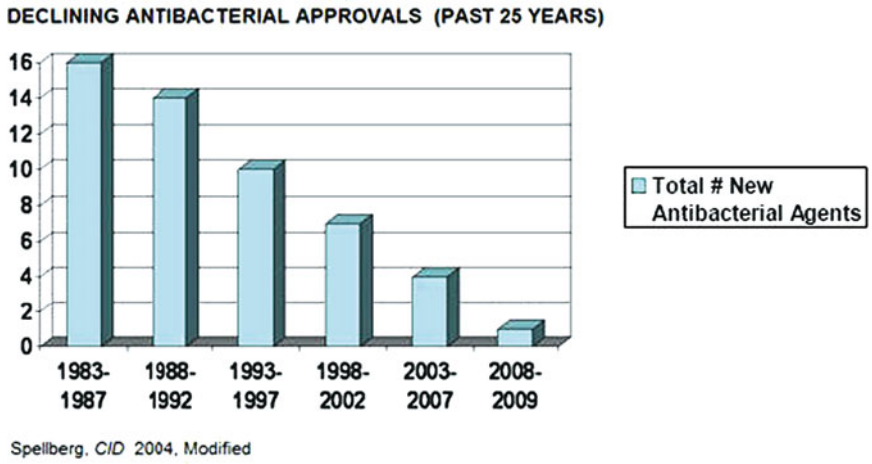

Fig. 4.2 Approval of antibiotics at the FDA over time. From the Infectious Diseases Society of America with permission

1983 and 2007 (Fig. 4.2). 2008–2009 is looking to be even worse. The Infectious Diseases Society of America, in their white paper, Bad Bugs, No Drugs, points out that between 1998 and 2004, only 10 new antibiotics were approved. In 2002, 89 new medicines were approved, but none of them were antibiotics. Since 2002, only eight new antibiotics have been approved with no approvals occurring in 2006 and again in 2008. This adds up to about one new antibiotic approved per year for the last 7 years compared to over three antibiotics per year between 1983 and 1987. Of six antibiotics submitted to the FDA between 2007 and 2009, only two have been approved. This represents a historically high late stage failure rate of 67% for antibiotics.

Does the FDA contribute to our lack of new antibiotics? In my opinion, the answer to that question is a resounding YES. Without significant changes from the FDA and perhaps from Congress, the lack of new antibiotics can only be expected to worsen. In 2002, Bob Moellering and I wrote an article in the journal Clinical Infectious Diseases entitled The FDA and the End of Antibiotics. In it, we expressed the concern that the uncertainty around requirements for clinical trial design, the tightening of trial requirements with its associated increased costs and the perceived hostility of the agency towards antibiotics would help drive more companies out of the area. Since then, unfortunately, our predictions have all been correct. Our antibiotic pipeline has only become drier and the number of companies active in antibiotics research has continued to dwindle.

How does the FDA contribute to the perfect storm for antibiotics? Guidance documents from the FDA can be helpful in that they tell everyone the kinds of things they need to do in order that the FDA will approve the product in question. They are currently issuing a series of guidances for the design of clinical trials for antibiotics

that make it difficult, and at times impossible, to actually carry out the proposed trials. But if these guidance documents mandate studies that are not feasible – where are we? Nowhere.

The FDA seems to be buffeted by political pressures that are frequently based more on rumor and innuendo than good science. They allow themselves the luxury of changing policy while sponsors are in the midst of multi-10s of millions dollar trials invalidating the very designs they agreed to at the start of those trials. They are inconsistent in their treatment of generic compared to branded antibiotics where the latter get much more scrutiny. The FDA does not always avail itself of the best advice even though, given their recent leadership, they need the best advice they can get.

One of the great things about antibiotics is that the tests we use both in the test tube and in experimental animals predict with a great degree of certainty whether the antibiotic will work in people or not. Once we know just a little bit about how the drug behaves in people, whether and how it is absorbed and distributed to human tissues, we can quickly, based on test tube and animal work, predict the correct dose to treat human infections. The FDA is very well aware of this. Included in the documents companies must submit to apply for permission to study the drug in patients, the FDA requires an entire section on how the company chose the dose they propose to study. This should remove a tremendous worry from companies, regulators, physicians and patients in the sense that we know that the antibiotic will work and we have a good idea of the dose that will be required in order for that to happen. Of course, we can't always predict human toxicity or metabolism with this degree of accuracy, so antibiotics can fail because of problems in those areas. They can also fail even if they work at the doses chosen, but they don't work as well as the antibiotics to which they are being compared in the clinical trials.

The FDA Increases Clinical Trial Design Stringency and Costs. Companies Abandon Antibiotic Research

In 1999, I was working at Wyeth Pharmaceuticals. Wyeth had discovered a new chemical series of tetracycline derivatives that was active against a variety of resistant bacteria including those resistant to the tetracyclines. We were getting ready to enter the last (and most expensive) stage of clinical trials prior to submitting our request for marketing approval. We followed the FDA guidelines in designing our trials. They allowed us to set the statistical stringency of the study, within limits, according to the size of the trial. Therefore, as the trial size got smaller, the stringency would be lower. In our discussions with the FDA, it became clear that they were going to require trials of a size and cost that was unprecedented for antibiotics being developed to treat patients in hospitals. The FDA was concerned that the kind of clinical trials used for approval of antibiotics in the past were not sufficiently robust. In these trials, since using a placebo is generally thought to be unethical, we compare the new, experimental antibiotic with an older, proven antibiotic. But, since

the older, comparator antibiotics (after the sulfonamides and penicillin) had never been compared to placebo (no active therapy) the FDA felt that there was a chance that new products might slip to a point of being ineffective. The issue is a statistical one (but has little to do with life as we know it!). When you compare two products in a trial, the two are compared statistically. This being the case – you can't really do an equivalence trial since to prove that two drugs are statistically equal requires an infinitely high number of patients. For antibiotics, you also would be hard pressed to do a superiority trial since the antibiotics work so well that proving superiority also requires a very high number of patients. It would also be hard to recruit patients into a trial where you know that the patient has a pathogen resistant to say the comparator antibiotic but not the new one given that the patient would have a random chance of receiving either drug. Therefore, all antibiotics since the 1950s have been studied in a so-called non-inferiority trial. In this sort of trial, you must accept some limit on the chance that the new drug is inferior to the standard approved therapy used as a comparator. That statistical margin is the problem. The tighter the margin, the more patients are required for the trial. In the past, as I noted above, margins were deliberately set to keep trials at a reasonable size. These margins, usually set somewhere between 10 and 20%, were acceptable to the FDA. 15% was a commonly used margin. That is, for seriously ill patients, the FDA would accept the possibility that the new treatment might be up 15–20% worse than the comparator. So, over time, in the worst case scenario for every drug, if one were 15% worse than the other and than that one became the comparator for the next and so on, the new antibiotics could end up being no better than nothing at all. Those of us actually treating patients with infections were always puzzled by this worry since we knew from the evidence of our own eyes that the antibiotics were effective for most serious infections. The FDA wanted us to reduce that margin to 10%. When you compare the patient numbers for the two circumstances, the 10% margin required more than twice the patients (and therefore about twice the cost) compared to the 15% margin. Remember, we are talking about a theoretic maximum difference between the two drugs, not the actual difference. So, while scientifically, it might be preferable to narrow this margin (why not to 5 or 2 or 1%?), the trials were going to cost more, expose more patients to an experimental drug and were going to take longer to perform. The time until the new therapy would be available to patients would be longer and the time to market for the new therapy would be more distant.

We presented the result of our discussions with FDA to Wyeth's senior management. When they saw the estimated costs for the FDA-proposed trials and the increase in time required, they balked. Our management was concerned that it would take too long for us to recoup the trial costs or that we might never recoup them. They put the entire program on hold.

We worked with Pharmaceutical Research and Manufacturers of America (PhRMA, the pharmaceutical trade and lobbying group) and with the Infectious Diseases Society of America representing infectious diseases physicians to open a public discussion with the FDA in hopes of salvaging our potentially important new antibiotic and to keep open opportunities for the development of other new

antibiotics. A series of workshops with all three, FDA, PhRMA and the Infectious Diseases Society were held during 2000 and 2002 to address FDA concerns. The result of these discussions was that the FDA did not make any blanket decision covering all antibiotics, but agreed to evaluate trial designs on a case-by-case basis.

In further discussions with Wyeth the FDA allowed Wyeth to proceed with 15% margins and tigecycline was developed and finally approved in 2005. Wyeth as it turns out, was one of the last companies to be allowed to use a 15% margin – almost everyone else since then has had to use a 10% margin for most indications.

Between 2000 and 2002, Roche, Lilly, Bristol-Myers Squibb and even Wyeth all announced they would discontinue research in antibiotics. Many more would follow closely on their heals. There are many reasons for this as we will discuss in Chapter 6, but one of the reasons certainly was the uncertainty around the FDA's clinical trial requirements and a feeling among many in industry that the agency was actually hostile to antibiotics in general.

One of the requests industry and the Infectious Diseases Society made to FDA in 2000 was that the agency modernize their guidance for the development of antibiotics so at least companies would know what kind of trials they would have to conduct to obtain approval. Since then, the agency has actually released a number of new draft guidance documents. The good news is that industry knows what it has to do. The bad news is that, frequently, they can't do it.

The first new guidance released indicated that all the old guidance documents on trial design for antibiotics were no longer considered valid by the agency. Next, the agency required a justification for the statistical margin that was to be used in proposed comparative trials. I think this was a way of getting sponsors to help FDA in doing some literature research in this area. The idea is that to define this margin, you have to define the benefit that the antibiotic would have compared to placebo. Since placebo controlled trials have not been done since the sulfonamides and penicillin, this gets to be a bit difficult.

With their advisory committee and in public, the FDA began to examine the issue of antibiotics used for mild infections like sinusitis, bronchitis and otitis (middle ear infections). The issue for these infections is that they frequently are caused by viruses and not bacteria and therefore would not respond to antibiotics in any case. This leads to much of the unnecessary use of antibiotics which in turn probably leads to antibiotic resistance. The other question is that even when bacteria cause these types of infections, will they get better without treatment? Will serious complications arise without antibiotic treatment? How do we know that antibiotics even work? The scientific literature is very conflicted on this subject. The area of mild infections is directly related to the agency's basic concern about comparative trials where a placebo is not used. How do we know that the standard or comparator antibiotic is better than no antibiotic?

"Mild" Infections Require Placebo-Controlled Trials – Industry Balks

Otitis media or middle ear infection might be the clearest example. These are the typical ear infections occurring mainly in childhood starting at around 6 months of age. Otitis media is painful and for many years clinical practice in the US was to treat them with antibiotics in the belief that killing the bacteria that cause the infection would result in more rapid relief of pain and would prevent potentially serious complications. Many parents in the US have had the experience of taking their sick child to their physician or to an emergency room for these infections. Some children who had repeated episodes were even given antibiotic prescriptions in a "just in case" sort of arrangement. If they had typical symptoms, they would call their doctor and start antibiotics until they could get into the office. It goes without saying that many antibiotics have FDA approval for their use in otitis media – all based on trials comparing one antibiotic with another and none with a placebo control. For the pharmaceutical industry, otitis was a very lucrative market.

However, a number of clinical trials comparing antibiotic to placebo were carried out, mainly outside the US, which seemed unable to show a clear advantage of antibiotic therapy over a simple prescription of a pain reliever. In some of these trials, it appeared that infections caused by one particular organism, *Streptococcus pneumoniae*, required antibiotic therapy for cure. But this organism only caused a minority of all otitis and there is now a very effective vaccine that protects, to a certain extent, against otitis caused by *S. pneumoniae*. Many studies later, it seems that the best approach is one of expectant therapy. The child is given a pain-reliever. If they still have symptoms after 2–3 days, an antibiotic is prescribed. In these circumstances, around 80% will not need antibiotics. There is no difference in any outcome between patients given antibiotics immediately and those treated expectantly. The agency now requires a placebo-controlled trial to prove that an antibiotic works in otitis. Given the data, we can agree that this is a reasonable requirement.

Some pediatric infectious diseases specialists disagree that patients with true otitis media do not need antibiotics. They argue that the diagnosis in many of the placebo-controlled trials that were carried out in the past were faulty and did not represent true bacterial infection of the middle ear. They claim that antibiotics can play an important role in shortening the duration of disease and preventing complications in true otitis media. This disagreement has led to an ongoing placebo controlled trial in Finland that is being funded by Finland. The patients are very carefully examined such that the diagnosis of otitis is not in doubt. This may be the first trial where there will be no argument about whether the patients actually have otitis and where there is an untreated control group. If this trial shows a significant benefit for antibiotics, it is possible that placebo controlled trials will be a thing of the past. If there is no benefit, of course, it will mean that for most patients antibiotics are not necessary. Whether such data would alter clinical practice and patient attitudes is another question.

The American Society of Pediatrics tried to promulgate guidelines suggesting that patients with severe symptoms, those age <6 months and those where the diagnosis is certain that it is otitis media be treated with antibiotics immediately. This leaves older children, those with milder disease and those where the diagnosis is less certain (the majority of patients) available for expectant therapy. In spite of these guidelines, recent surveys have shown that only 15% of children in the US are treated expectantly. That number should be about 85%. The most common reason is parental concern (85% of parents) about not using antibiotics. In addition, physicians prefer to treat based on probability of infection as opposed to certainty. One approach some physicians have been taking is to give the parents a prescription to fill in case the expectant therapy – pain reliever – isn't enough. That way, the parent controls the destiny of their child and themselves, the doctor has provided specific therapy, and everyone is satisfied.

The major need for new antibiotics in pediatrics today might be for those children allergic to the penicillins and their relatives. Many of the pathogens that cause otitis are resistant to the other types of antibiotics approved for use in children with otitis and clinical failures do occur because of these resistant organisms. I asked a highly respected colleague working in pediatric infectious diseases how he handles this dilemma. Simple, he replied, I just use a quinolone antibiotic. He believes at least one of them is safe for use in children even though they have never been approved for treating otitis in children and other pediatricians and the FDA have expressed safety concerns about the use of quinolones in children.

Given this state of affairs, I doubt that industry will attempt to develop new antibiotics for otitis in the foreseeable future. Of course the market loss for industry is a large one. But the reduced pressure selecting for resistance by unnecessary use in otitis is a benefit for new antibiotics developed for other kinds of infections.

Sinusitis is also a large potential market for antibiotics and is more controversial. As is the case for otitis, many antibiotics are already approved by the FDA and marketed for the treatment of sinusitis based on comparative trials. According to the American College of Physicians, in most cases, antibiotics should be used only for patients with the specific findings of persistent purulent nasal discharge and facial pain or tenderness who are not improving after 7 days or those with severe symptoms regardless of duration. This recommendation is based on a number of placebo-controlled clinical trials where a modest benefit from therapy either in terms of cure or in decreasing length of illness was mostly offset by an increase in adverse effects by the antibiotics when compared to placebo. The FDA has responded to this by saying that, given the modest treatment effect, they would be unable to judge, statistically, whether a given antibiotic was inferior or not to placebo in the absence of a placebo control. However, since not treating patients with severe symptoms or symptoms lasting more than 7 days goes against medical guidance, it is difficult if not impossible to carry out the placebo controlled trials mandated by the FDA. The industry is staying away from this one. If we wanted a new antibiotic now or in the foreseeable future for the few cases of acute bacterial sinusitis that might be caused

by resistant strains of bacteria, we would be disappointed. Again, like otitis, this was previously a large market segment for the pharmaceutical industry that has now virtually disappeared for new products.

Finally, there is bronchitis. This is a really controversial area. Patients with chronic lung disease, specifically, chronic obstructive pulmonary disease or COPD, have ongoing breathing problems and other symptoms like productive cough that get worse (exacerbations) from time to time. They are chronically colonized with bacteria in many cases. That is, even when they are not experiencing worsening symptoms, they have bacteria living in their lungs. Their exacerbations seem to be associated with the acquisition of new strains of bacteria in their lungs. For many years, physicians have thought that treating the bacteria isolated from the sputum (bronchial and lung secretions these patients cough up) of patients at the time of an exacerbation would shorten the duration of the episode and help avoid more serious complications like respiratory failure and pneumonia. Like otitis and sinusitis, many antibiotics marketed today are indicated for the treatment of these exacerbations all based on comparative trials without placebo controls. We now know that for so-called mild to moderate exacerbations, antibiotics appear to offer little advantage compared to no antibiotics. However, for more severely ill patients, studies suggest that antibiotics have an important role in reducing relapses, complications and in reducing mortality. According to the Cochrane Review, an analysis of many placebo-controlled trials for this disease showed a clear benefit for antibiotic treatment.

> For COPD exacerbations with increased cough and sputum purulence antibiotics, regardless of choice, reduce the risk of short-term mortality by 77%, decrease the risk of treatment failure by 53% and the risk of sputum purulence by 44%; with a small increase in the risk of diarrhoea. . . . . this review supports antibiotics for patients with COPD exacerbations with increased cough and sputum purulence who are moderately or severely ill.

Again, the FDA, in spite of this sort of information, has required placebo-controlled trials for new products. Since it might not be ethical to withhold antibiotics from patients with severe exacerbations and since antibiotics might not work as well for mild disease, only one pharmaceutical company has yet ventured into this area. Their trial did show a benefit for their antibiotic, but failed to recruit a sufficient number of patients to satisfy the FDA. They went out of business shortly after their trial was stopped. (see Chapter 6 for more details). For patients and their physicians, this will mean no more new antibiotics for bronchitis. For the industry, another market has been closed. There are academic investigators attempting to conduct a placebo-controlled trial for bronchitis with funding from the NIH, but it is not clear how severely ill the patients are who are included in the trial. No data has, as far as I know, yet been published on the ongoing NIH sponsored trial.

Here are three indications where physicians perceived that there was a routine requirement for antibiotics and where that perception has been called into question. It also seems clear that, at least in some circumstances, for sinusitis and bronchitis,

antibiotics are useful and in the latter case may even save lives. If we as a society agree (I do) that our current antibiotic armamentarium is sufficiently robust and that bacterial resistance is not a problem in these diseases, then I guess there is no need to further question the FDA's current stance. Unfortunately, since, in order to develop new drugs, the industry has to think 7–15 years ahead, if antibiotic resistance were to arise as a problem for, say bronchitis, we would be without important new therapeutic options for years to come.

New Antibiotics for Mild Infections Are Forced from the Market While Generic Antibiotics Are Still Approved in the Absence of Placebo-Controlled Trials

The Ketek Scandal

As I noted earlier, there are lots of antibiotics, including penicillin, approved for otitis, sinusitis and bronchitis based on the old approach (comparative rather than placebo-controlled trials). Some of these older antibiotics even have some level of toxicity. According to the FDA's own calculus, these products have a risk:benefit ratio of zero since their benefit has never been shown using superiority or placebo-controlled trials. Has the FDA moved to remove marketing approval for these indications from these older antibiotics? No. This point was driven home recently by the scandal over the FDA handling of a new antibiotic, Ketek (telithromycin). Even Congress got involved. This is a story I have followed closely and I was present at the final FDA meeting dealing with this new antibiotic. The Ketek story illustrates the effect of political pressure on the FDA process, FDA's inconsistent treatment of branded compared to generic antibiotics, and, in my view, their lack of leadership in general.

Ketek, or telithromycin, is an antibiotic designed to overcome antibiotic resistance in respiratory pathogens. It provides an important alternative to therapy for patients who are allergic to the penicillin type antibiotics or who cannot tolerate the quinolone antibiotics. In 2004, Ketek was approved by the FDA for use in community-acquired pneumonia, acute bacterial sinusitis and in acute bacterial exacerbations of chronic bronchitis. At the public meeting to discuss Ketek, held in Silver Spring, Maryland December 14–15, 2006, the FDA positioned Ketek as an antibiotic of questionable efficacy for the treatment of acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis, since approval was granted based on non-inferiority rather than placebo-controlled trials. They described rare but serious side effects including cases of severe liver toxicity attributed to Ketek. In this context, the FDA asked their advisory committee to weigh the risk to benefit ratio of Ketek in sinusitis and bronchitis.

Ketek is an antibiotic distantly related to erythromycin. It has the advantage of being active against erythromycin-resistant strains of bacteria.

Erythromycin-resistance (also resistance to azithromycin (Zithromax) and clarithromycin (Biaxin)) is a big problem among bacteria that cause respiratory infections like otitis, sinusitis, bronchitis and pneumonia. It has been shown that such bacteria do not respond well to therapy with the usual macrolide antibiotics like zithromax and biaxin. Ketek would then be a good choice for such patients where they might have a penicillin allergy or they might be unable to take the other major class of antibiotics for these infections, the quinolones like levofloxacin (Levoflox).

Ketek was approved in 2004 after a long regulatory history where several toxicity signals were seen in the late stage (Phase III) trials. However, post-marketing surveillance, primarily in Europe, but also in other ex-US countries where Ketek had already been sold for a number of years, showed no substantial safety problems during almost 4 million courses of therapy. Thus the agency approved Ketek for treatment of community-acquired pneumonia, sinusitis and bronchitis.

This was a scandal-ridden approval. In their analysis of the data for Ketek in 2001, the FDA requested additional safety data from the sponsor (Aventis at that time). The FDA was particularly concerned about possible liver toxicity, cardiac toxicity and visual effects that might be associated with Ketek. Aventis then carried out a 24,000 patient safety trial of Ketek. To my knowledge, this remains the largest such trial ever performed by the industry and it was performed in record time – about 1 year. Of course, the size and speed of the trial must have stretched Aventis' resources to the breaking point. This trial was so tainted by fraud among clinical investigators, one of whom was convicted and imprisoned, and by other issues with the data per se, that the FDA declared it would be unable to use any of the data for approval. This was clearly a trial too big for its britches.

It was then that the FDA turned to the voluntary safety reporting system maintained by countries where Ketek had been approved and where the drug was already marketed. This was clearly a deviation from standard FDA practice. Critics charged that since the database used was a voluntary one and was known to underestimate toxicity, it could not be relied upon for approval. A key FDA safety officer declared at the 2006 meeting that accepting the data collected by Europe was tantamount to accepting data collected by third world countries. An FDA medical officer became a whistle-blower leaking documents and internal e-mails. He accused his supervisor of inappropriately using the controversial 24,000 patient safety study in consideration of approval and of inappropriately pressuring the staff writing reports and opinions during the approval process. He further noted that the FDA knowingly failed to disclose key issues of fraudulent data to their advisory committee in 2004. The FDA supervisors responded that they were unable to do so since there was an ongoing investigation into fraud and that the enforcement arm of the FDA restricted them to silence on this issue.

Of interest, a representative of the European regulatory agency (EMEA) was present at the 2006 FDA meeting and presented data from Europe and recent European decisions related to Ketek. In Europe, approved drugs are routinely re-examined on a regular basis. (We will come back to this in our chapter on Modest

Proposals, Chapter 7). The European Medicines Agency (EMEA – the FDA for Europe) had just completed its review of Ketek including substantially more safety data than was available at the time of the 2004 approval of Ketek by the FDA. Based on its review, the EMEA approved continued marketing of Ketek for all its indications for an additional 5 years.

Since the approval of Ketek in 2004, as noted earlier, the FDA has concluded that comparative trials (used for approval of every antibiotic in history for every bacterial respiratory infection studied to date) are not sufficient to prove efficacy for otitis, sinusitis and bronchitis. Placebo controlled trials are now required. Thus, since Ketek had not demonstrated efficacy in sinusitis or bronchitis in this way, the FDA asked advisors to help determine if the risk:benefit ratio for Ketek justified continued marketing for its approved indications. Obviously, if you believe that the trials completed cannot prove that the antibiotic was effective, any safety risk is logically unacceptable.

The FDA undertook its own analysis of the voluntary database that tracks physicians' reports of adverse events for marketed drugs. Their own analysis of the risk of liver toxicity caused by Ketek as determined by data mining of the reporting system database suggested that the compound was associated with no more risk than other, older antibiotics or than Tylenol. Serious liver toxicity from Ketek was estimated to occur 1 in 100,000 to 1 in 200,000 courses of therapy. To put this in perspective, fatal allergic reactions from the penicillins occur with a frequency of 1 in 50,000 to 1 in 67,000 courses of therapy, and serious reactions occur as often as 1 in 7,000 courses of therapy. Amoxicillin-clavulanic acid (Augmentin) (a penicillin analog) is the biggest selling antibiotic in history with peak year sales of around $2B. Augmentin is now generic. It also causes more cases of serious liver toxicity than any antibiotic on the market including Ketek. But the penicillin drugs including Augmentin are still frequently used to treat sinusitis and bronchitis with the continuing approval of the FDA. Tylenol is one of the most widely used drugs in the world (although not an antibiotic) and causes more cases of acute liver failure requiring liver transplant than any other drug. It is still sold without prescription worldwide. The advisory committee voted for withdrawal of marketing approval of Ketek for sinusitis and bronchitis at the meeting. The FDA followed their advice shortly after the 2006 meeting.

During the scandal leading up to the 2006 advisory committee meeting, Senator Grassley and Representative Markey were threatening a full-scale congressional investigation of the approval of Ketek. They seemed to suspect that the agency was somehow in cahoots with industry in general or with Aventis in particular or was simply incompetent. The FDA anti-infectives group went into defense mode and was working many extra hours and days supplying materials to congressional staffers. It is possible if not likely that the entire 2006 advisory committee meeting was a response to this political pressure. In fact, the pressure seemed to dissipate after the advisory committee meeting and with the reassignment of the Director of the Divison of Anti-Infective and Ophthalmology Products at the FDA.

Pneumonia – The New Frontier. New Trial Requirements for Pneumonia Will Make Approval Much More Difficult and Costly and Sometimes Simply Infeasible

Along the same lines as their inquiry on otitis, sinusitis and bronchitis, the FDA recently examined the role of antibiotics in pneumonia. Those of us in the infectious diseases community held our collective breath waiting to see if the FDA would decide that they did not understand whether antibiotics had an effect on bacterial pneumonia. To us clinicians, that antibiotics have a dramatic beneficial effect in the treatment of pneumonia was obvious and well proven by our own personal experiences as physicians and by clear historical precedent. Many of us could not understand what the FDA was thinking.

Pneumonia is generally divided into two categories – infections acquired in the community and those acquired while in the hospital. Both can be lethal. Community-acquired pneumonia strikes four to six million Americans every year. 600,000 are hospitalized and tens of thousands die leading to an annual cost to the US of over $10 billion.

In order to begin to understand the importance of antibiotics in the treatment of pneumonia, we have to delve back into history. When antibiotics were first developed in the 1930s (sulfa drugs) and the 1940s (penicillin), clinical trials as we know them today were not performed. Physicians would treat patients with the antibiotic and then search among hospital records for other, similar patients who were not treated (historical controls) or they would compare treated patients to similar patients in the hospital at the same time but who were not treated (concurrent controls). Obviously, this is not the same as asking a patient to agree to be either treated or not in a blinded fashion such that neither the patients nor the treating physicians know who is on which therapy as we would do in a contemporary trial. Nevertheless, when we look at deaths from pneumonia in these older studies, antibiotics prevented anywhere from 16 to 26% of them.

This analysis is not as straightforward as we would like. Community-acquired pneumonia has a variety of causes and not all of them are treated well with penicillin or sulfonamides, the antibiotics studied in the 1930s and 1940s. Some cases are actually due to viruses that are not treated by antibiotics at all. Even so, antibiotics still prevented 16% of deaths in all comers in those early studies. Table 4.1 below has been modified from the position paper presented by the Infectious Diseases Society of America to the FDA in 2008.

Table 4.1 Historical Studies of Antibiotics (penicillin or sulfonamides) in Patients with Pneumonia

	Untreated mortality	Treated mortality
Historical-control Studies	2184/5747 (38%)	398/3293 (12%)
Concurrent-control Studies	58/254 (23%)	21/308 (7%)

In other studies, if we look at only those patients who were infected with the most common bacterial cause of pneumonia, *Streptococcus pneumoniae*, and among those we look only at those patients that had invasion of the bloodstream by the bacteria (10–20% of patients), penicillin or sulfonamide prevented anywhere from 30 to 80% of deaths. If we don't look at deaths, since very few patients die from pneumonia today (because we have such good antibiotics in large part), but we rather look at time to normalization of temperature, we get a different perspective. In one study of sulfonamides from the 1930s, 84% of antibiotic treated patients were afebrile by 72 h compared to 2–3% of untreated patients. Clearly, antibiotics work and they work well. The overall mortality for pneumonia today, taking all comers in clinical trials, is around 3%. Any physician who has treated a patient with bacterial pneumonia can testify to the dramatic effect of antibiotics in this disease (see Chapter 2).

Do we need new antibiotics for community-acquired pneumonia? Probably not today. Our antibiotic armamentarium is diverse enough given the emergence of resistance that we are seeing that, in my own view, there is not an urgent need today for new antibiotics to treat this disease. The problem is that we have to think 7–15 years into the future. The risk is unpredictable. Who would have predicted the epidemic of vancomycin-resistant enterococci that has devastated our intensive care units since 1989? My crystal ball is telling me that in 10 years, having a new antibiotic for this disease would be worthwhile, especially for those patients allergic to the penicillin type drugs, given today's rate emergence of resistance to the non-penicillin type antibiotics. Of course, today if you are one of those rare individuals who can take neither the penicillins nor the quinolone antibiotics, you still have Ketek, which remains approved for pneumonia.

What has the FDA decided about community-acquired pneumonia? Who knows as of this writing? They have issued draft (I emphasize draft) guidelines that, in my view, will make it extremely difficult if not impossible to carry out clinical trials in this disease. First, they require that no prior antibiotic be given. Scientifically, this is a sound decision since even a single dose of antibiotic can have a beneficial effect in pneumonia. In one recent trial, an antibiotic that was later found to be ineffective for pneumonia because it is actually inactivated in the lung looked successful among patients that had up to 24 h of effective prior antibiotic therapy but was clearly much less active among patients who had no prior therapy. Therefore, any experimental drug given after an effective antibiotic, even after only one or two doses, might look better than it really is. In fact, in recent trials, about 40% of patients had received at least one dose of another antibiotic before being enrolled in the trial. If those 40% had to be replaced with those who had no prior antibiotic, the trial would take much longer. For more serious cases of pneumonia, such as those now required by the FDA, it will be even harder to find patients with no prior antibiotic at all. Further complicating this requirement is a quality measure used for hospital accreditation for continued participation in Medicare and other reimbursement plans. This quality measure requires that the first dose of antibiotic be given for pneumonia within 6 h of the patient first being seen in the health care facility. Clearly, this will make it even harder to find untreated patients to enroll in clinical trials of antibiotics for

pneumonia. The best solution to this problem is to allow only one or two doses of a prior antibiotic before entering patients into a trial for a new treatment. That would preserve most of the scientific integrity of the study and still allow a reasonable rate of enrollment. The analysis at the end of the study can then be stratified looking separately at those who had received prior effective therapy and those who had not. This approach would be a balance between perfect science and reality – a concept that seems to have escaped the FDA.

Second, the number of patients required has skyrocketed into the thousands further increasing the cost and the time it will take to run such a trial. The FDA has required that the new antibiotic demonstrate that it works only in those patients that have a documented (by culture) bacterial infection. Overall, in America, the number of cases of pneumonia that are documented by isolating the infecting organism is an astounding 7.5% (Medicare data). In recent clinical trials where we make heroic efforts to identify the bacterial pathogen, the diagnosis rate varies from 20 to 35% with an average of about 25%. Given these numbers and the FDA's statistical requirements, to gain approval of an oral drug for pneumonia would require studying over 5000 patients. My estimate is that the trials alone would take more than 5 years and that the data might be obsolete by the time the FDA actually approved the drug. The Infectious Diseases Society and the FDA recently held a workshop to discuss the use of modern diagnostics to boost the proportion of cases where the pathogen could be identified. It is clear that this is not an attractive market for diagnostics companies and that the pathway to approval for such a diagnostic test is not straightforward. One diagnostic company executive openly questioned whether "the juice is worth the squeeze." The only other way forward offered by the FDA that was at all practical was to propose the use of an investigational diagnostic method that would have to be considered on a case be case basis and where the implications for how the company would be able to promote the drug after using such a diagnostic test was unclear. The company might be stuck having to promote their antibiotic to be used only after a diagnosis had been established with an unapproved investigational diagnostic test. The design proposed by the FDA is quite simply not feasible in today's world and no pharmaceutical company will undertake such a study.

Finally, the severity of illness to be treated has increased. There is some belief that patients with the mildest forms of pneumonia are more likely to get better without antibiotics, so the FDA would like to eliminate them as much as possible from clinical trials so that the antibiotic being investigated is appropriately challenged. The science behind this decision is, at best, controversial and this requirement will further slow trial enrollment rates and increase costs. Mild pneumonia tends to get worse without treatment.

Some of these FDA requirements may be scientifically justified, but they will help to assure that no or only very few new antibiotics will be developed for this important infection.

To make matters worse, Public Citizen has publicly called for a different endpoint altogether for studying community-acquired pneumonia – that of mortality. The proposal is scientifically based on the fact that the benefit of antibiotics in pneumonia was proven by looking at mortality rates in treated compared to untreated

patients in the 1930s and 40s. This approach is completely irrelevant in the antibiotic age. The problem with this suggestion is that almost no one dies of pneumonia anymore because our therapy is so good – especially when considering the more common forms of pneumonia. Overall, for community-acquired pneumonia treated as an outpatient, the mortality ranges from 0.1 to 0.9%. For pneumonia that requires that the patient be hospitalized, it ranges from 0.9 to 26.7% – but those patients in the high mortality range are those admitted to the intensive care unit where antibiotics may not be much help anymore. These ICU patients usually have severe mechanical problems with their breathing from all the fluid in their lungs and other derangements. The overall mortality in trials of patients with community-acquired pneumonia is around 3%. So the proposal to use mortality as an endpoint for studying pneumonia would require enrolling from 7200 to over 100,000 patients in a trial. Again, this is a completely infeasible design.

PhRMA has an antimicrobial working group that has provided a response to the FDA's new proposed guidelines for clinical trial design in pneumonia. They have made suggestions that respond to the FDA's requirement for strong science and for microbiologically documented infection while providing for the feasibility of future trials. Because the industry is thought of as the devil incarnate in Washington and around the nation, politically, the FDA has no particular incentive to listen to them.

In fact, there was such a negative response to the FDA's draft guidelines for community-acquired pneumonia that they held yet another Anti-infectives Drug Advisory Committee (AIDAC) meeting in December of 2009. I was one of the presenters at the meeting. Prior to the meeting, I had submitted my presentation materials showing that the FDA had mandated clinical trial designs that were infeasible. I pointed out that this was, in a way, irresponsible and misleading. They seem to have heard that message because in their summary, they recognized that the issuance of guidance requiring infeasible trials was not acceptable. The FDA also recognized that mortality was not the only acceptable endpoint for a clinical trial of pneumonia and they agreed with the world of physicians who said that one could tell whether a patient was responding to antibiotics for pneumonia by day 3 of therapy. These concessions could be a major turning point in our discussions with the FDA. I (and others, too) have communicated a trial design strategy that would allow for feasible trials and still achieve everything the agency would like in pneumonia. But I have been disappointed so often in the past that I won't break out the champagne until I see new guidance with feasible trial design requirements.

The FDA Can Change Its Requirements After Completion of a Trial and then Require New Trials for Approval

Another really interesting development at the FDA is the policy that they can change their minds about previous agreements. In the old days, maybe even up to 7 years ago or so, if you had a discussion with the FDA on your trial design and they agreed with it in writing, they would not reject your data because they had come out with

new policy requiring a different design. This is important. A company will pay about $30 million for a single Phase III antibiotic trial. To get approval, you need to run two such trials for each indication (skin infection, pneumonia, etc.). These trials usually take about 2 years to run and at least another 6–12 months for data analysis and submission of the dossier to regulatory agencies. Most companies plan on spending about $70 million on trials and other requirements to get approval for a single indication. Before putting that much money in play, companies like some reassurance that the trial design they are using will, if the study reaches its endpoints, lead to approval by the FDA. There is a process in place at the FDA (Special Protocoal Assessment or SPA) where sponsors can submit specific trial protocols and get written comments back from the FDA. This, in the past, was extremely valuable to all parties. The withdrawal of approval of Ketek for sinusitis and bronchitis because they did not run placebo controlled trials that they didn't know they needed to run is one example of how the exchange between industry and the FDA has become dysfunctional. In 2005, Advanced Life Sciences started Ph. III trials of their antibiotic, cethromycin, which they had licensed from Abbot a number of years earlier. It is similar to Ketek, but thought to have a better safety profile. They agreed a trial design with the agency and completed their trials in 2007. An NDA (New Drug Application for approval to market) was submitted to the FDA and accepted by them in 2008. In 2009, the FDA informed Advanced Life Sciences that the trial data submitted did not prove that their drug was efficacious because the design and therefore results did not conform to guidelines promulgated by the agency in 2009. Advanced Life Sciences is now in the throes of trying to complete such a trial. Their drug will now be delayed by years if it ever does get approved.

An even more abysmal example of this occurred just after Thanksgiving, 2009 when the FDA notified Theravance that the data from two phase III trials in hospital-acquired pneumonia would have to be analyzed based on a primary endpoint of all cause mortality and not the previously agreed primary endpoint of clinical outcome. Theravance had designed these two trials to look at clinical improvement in the actual pneumonia being treated as a primary endpoint and examined all cause mortality as a secondary endpoint as agreed with the FDA at the outset of the studies. If Theravance is unable to provide enough data to satisfy the FDA statistically that they succeeded in improving the new primary outcome of all cause mortality, they will have to run at least one more study in this indication. I would estimate that trials in hospital-acquired pneumonia probably run around $50 million each because of the complexity of the patients and the severity of the illness involved. So Theravance and its partner Astellas have probably already sunk $100 million into these trials and they may have to sink yet another $50 million to get to the new goalposts – and this will only be after at least another 2–3 years of study.

Another company, Replidyne, went belly-up following a similar change of opinion in midstream by the FDA. If companies cannot have some assurance that the large investment required up front for clinical trials of antibiotics won't be thrown down the toilet from the get-go because the FDA can change the goalposts at any time, why should they take the risk at all? This is especially true now when the goalposts seem to move every month!

The FDA is Regulating Itself Out of the Antibiotics Business

How did the FDA get where it is? The FDA started by trying to justify the statistical margins used to demonstrate that one antibiotic (the new one under study) was not inferior to the antibiotic used as a comparison – the so-called gold standard therapy. We have to design our trials that way because to use a placebo for patients with infections would, in most cases, be unethical at best and criminal at worst. The margin defines statistically how inferior in the worst case the new antibiotic might be. This does not mean that the new antibiotic might actually be that much inferior (10–15% in most modern studies) but that this is the limit beyond which the FDA will not go in approving the drug. So, in recent years, the FDA has been scratching their heads trying to find justifications for defining these margins. The idea is that the underlying assumption when you say that one antibiotic is not inferior to the other is that the standard to which you are comparing the new drug is still better than no antibiotic at all. Of course, to us infectious diseases physicians, this is patently obvious and we don't need statistics to tell us that antibiotics work. But apparently the FDA does. The FDA then searches for historical data coming from the days – 80 years ago – when antibiotics were studied in comparison to no therapy. The endpoint used in those studies was mortality. To be scientifically consistent, the FDA always heads back to these 80 year old studies and seems to want us to keep doing things the way they were done back then, even though 80 years have passed and both the data and the methods are no longer scientifically relevant. This must change if we are ever to make any progress in developing and approving new antibiotics.

Table 4.2 below shows indications and whether or not the trials required by the FDA are feasible or not. Also shown is my own view of the industry's opinion

Table 4.2 Indications for marketing approval available from the FDA vs. current feasibility of trials in those indications

Indication	Are trials feasible	Market attractive
Skin infections	*Yes*	*Yes*
Community-acquired pneumonia	*No?*	*Yes*
Hospital acquired pneumonia	*No? awaiting guidance*	*Yes*
Ventilator associated pneumonia	*Yes – awaiting guidance*	*Yes*
Intra-abdominal infections	*Yes*	*Moderate*
Urinary tract infections	Yes	No
Bone and joint infections	No	Maybe
Heart valve infections	No	No
Fever in neutropenic (patients with low blood counts post chemotherapy) patients[a]	*Yes*	*Yes*
Otitis media	No	Yes
Acute bacterial exacerbations of chronic bronchitis	No	Yes
Acute bacterial sinusitis	No	Yes
Pharyngitis (strep throat)	?	No

[a]May no longer be considered a valid indication in Europe

on whether the market opportunity for a given indication is reasonable. I was able to identify only five indications where trials are still feasible and where industry still considers the market opportunity to be reasonable and these are indicated in italics in the table. The FDA is now considering guidance on clinical trial design for serious skin infections and for pneumonia acquired in the hospital. For both of these types of infection, but most especially for hospital-acquired pneumonia, there is a desperate need for new antibiotics now. If the FDA makes decisions that limit our ability to bring antibiotics forward for these infections, we will all pay a high price. And, at that point, there will essentially be no infections for which we can actually develop new antibiotics. The industry will simply pull out altogether (if they have not already done so).

In addition to the loss of commercially interesting indications for antibiotics, there is the rapidly changing pharmaceutical marketplace to consider. We will examine this from the industry point of view again in the next chapter. But consider the following. The US used to account for over 50% of the worldwide pharmaceutical marketplace. In 2009, the IMS estimates that the US will account for a record low 40% for a variety of factors we will consider later. But, for the FDA, this means that they are now less relevant in the world market than they used to be.

So it is quite possible that the FDA regulators will successfully regulate themselves out of their jobs.

We Need Balance and Perspective from the FDA

Back in 2000, when I was working for Wyeth and we were first presenting our views on clinical trial design in antibiotics to the FDA, we asked for a balanced approach. We all agree that the clinical trials upon which approval are based have to be scientifically sound and that the antibiotics we study must be appropriately challenged, must show good activity in the infections we are studying and they must be safe. The balance is required in that the ultimate trial design that we agree upon must be achievable within the resources and budgets that we have for antibiotics. I personally would also like to see some balance in the application of new guidance between new drugs and older drugs. If there is a risk of toxicity that we are not willing to accept for a new drug, why should we accept it for a much more widely used (and therefore more dangerous) older drug? We obviously have a long way to go.

One of the things I learned early on in my career, the first time I participated in the conduct of a clinical trial, was that clinical trials have little to do with life as we know it. As a physician, when I am confronted with a patient who might have a serious infection, say pneumonia, I can't not treat him or her because they are so sick they might not live more than 4 or 5 days or their kidneys are not functioning well or because they might also be infected with HIV, the virus that causes AIDS. I treat the patient as best I can and hope. But in a clinical trial, such a patient would frequently not be studied. Why? There are lots of reasons. If the patient in fact died

before the minimum length of therapy, the data could not be used since for either the experimental drug or the comparator. The treatment has to be long enough that we can evaluate whether it was successful or not. HIV infected patients might be harder to treat since they might not have a normal immune system. These all may be good reasons for excluding our hypothetical patient, but they also explain why trials are not real life.

Another disconnect between clinical trials and life on the wards is the fact that most, probably 70–80%, of initial antibiotic therapy is empiric. By that I mean that either the physician does not know the bacteria he/she is treating or, sometimes, doesn't even know the site of the infection (lung, urinary tract, etc). He/she just knows that the patient has a fever or other signs of infection that needs treatment. Usually, such a patient will be treated expectantly with an antibiotic or even more than one antibiotic to make sure that all the likely bacterial pathogens are treated. Only later, if a bacterial pathogen is identified or the site of infection declares itself, might the antibiotic therapy be more specifically tailored to the specific infection at hand. When I was consulting at the VA hospital, more often than not, if the patient had responded to the broad-spectrum therapy that was used initially, there was a great reluctance to change to a more specific therapy even when a specific pathogen had been identified. There is always a lingering doubt that maybe what was identified is not the entire answer. I frequently get the feeling that the FDA has lost sight of these issues and they actually believe that the trials they require reflect clinical practice. We will return to this subject in Chapter 7.

The FDA Makes It Difficult for Them to Obtain Good Advice

The FDA works closely with advisory committees. The FDA's Office of Antimicrobial Products has a Anti-Infective Drugs Advisory Committee (fondly known as AIDAC) that it uses to help its reviewing divisions with decisions around approvals, withdrawals, questions of trial design and other important issues that require public airing. There is also a strict conflict of interest policy that limits or bans the participation of individuals with a financial interest in the particular decision or decisions the committee confronts. The guidance actually speaks about a $50,000 limit that, in my view, is too generous. In its application of these policies I think the FDA has at times gone so far as to limit the expertise of its anti-infectives committee. The problem is that industry, like the FDA, needs outside advice. If folks in industry had no one to speak with other than themselves, I'm not sure we would ever have any products. These same experts can also provide valuable advice to the FDA. The anti-infectives world is a very small one and shrinking all the time. I once complained to the director of the anti-infectives reviewing division at FDA about the quality of the anti-infectives advisory committee. I felt that very few on the committee were experienced in antibiotics per se and especially in clinical trial conduct and design for antibiotics. These topics were almost always part of the committee discussions. She did not disagree with me and asked me for recommendations for

new committee members. She said they could not work with people in industry outside the single non-voting member that is a part of every advisory committee. She wanted nominations for women, professionals of color, and people from regions other than the Northeast. As I considered the people I thought had the experience and expertise the FDA needed at the time, I came up with a list of names – almost all white men from the East coast. None were appointed.

This discussion reminds me of a recent set of news articles noting that Senator (retired) Tom Daschle works for a lobbying firm tied to the health insurance industry while he is simultaneously a close advisor to President Obama on health care reform. Is this an apparent conflict of interest? Sure. Is President Obama able to put this in perspective when discussing things with Mr. Daschle? Of course. FDA scientists and reviewers are not stupid, either. They know how to sift advice. As long as everyone discloses his or her potential conflicts, a conversation can take place.

The FDA still works with outside stakeholders such as PhRMA and the Infectious Diseases Society of America and others. Unfortunately, good advice from all is frequently ignored.

What has happened to the FDA since 2000? The FDA was leaderless for most of the last 9 years. Either the appointed commissioners did not last long or there was an acting commissioner for most of this time. In the anti-infectives group, there has been a significant loss of key individuals in leadership roles who understood the more practical problems of trial design and struggled in tandem with industry to achieve both the FDA's charge of assuring efficacy and safety of marketed products and industry's goals of doing so in a feasible way. With a new and dynamic commissioner, I hope we will see a more balanced approach to antibiotics such that we will be able to have them when we need them.

See the Chapter 7 for suggestions on possible ways forward for us all.