PHARMACEUTICAL INVENTIONS AND THE LAW
A Study In Diseases, Drugs and Law Suits

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In the mid 1960s the pharmaceutical industry embarked on an enormous bout of Patent Litigation. The participants included most of the best known pharmaceutical companies and the subject matter consisted of some of the best-selling drugs of the day. These included such antibiotics as penicillins, cephalosporins and tetracyclins as well as novobiocin and porfiromycin, the tranquilizers librium and valium, several oral contraceptives, diuretics, antidiabetics, the antibacterial agent trimethoprin and finally a treatment for gout. In some cases, the litigation was on a relatively small scale, but in others it had a truly world-wide character with corresponding litigation in most westernised countries of the world. The most bitterly fought was probably that concerning Librium and Valium in which even the Courts were shocked at the fury with which the parties attacked each other. The prize for the longest single hearing goes to *American Cyanamid* v. *Ethicon* which concerned surgical sutures, which I count as a pharmaceutical for present purposes. This case, having gone to the House of Lords (where it provided the leading English authority on interlocutory injunctions), then came on for a trial which lasted for no less than one hundred and three sitting days spread over the greater part of a year. However, even this paled into insignificance compared with the penicillin litigation which comprised no less than three world-wide fights known affectionately to those who practise in the area as World War 1, World War 2, and World War 3.

In World War 1, the patentees of the penicillin ampicillin sued the manufacturers of the related penicillin hetacillin. In Australia, the case provided the leading High Court authority on interlocutory injunctions, known to lawyers as *Beecham Group Ltd.* v. *Bristol Laboratories Pty. Ltd.* It deals with the same questions as the *American Cyanamid* case in the House of Lords. In England, World War 1 went up and down through the court system like a yo-yo. It started in the High Court on an application for an interlocutory injunction which was refused and then allowed by the Court of Appeal on appeal. It

then went back to the High Court for trial, back on appeal to the Court of Appeal and finally reached the House of Lords. The whole process lasted from March 1967 to January 1977. Nor was this the end of the story, because as part of World War 1 the parties engaged in further litigation concerning a contract between them and this too went successively to the High Court, Court of Appeal and House of Lords.

Meanwhile, World War 2 had broken out between substantially the same parties. This concerned a penicillin called ampicillin trihydrate. World War 2 went to the Patent Appeal Tribunal, then to the High Court, the Court of Appeal, the House of Lords and back to the Patent Appeal Tribunal again.

World War 3, which was concerned with a penicillin called amoxycillin, involved probably the most interesting legal point of all. The case started off in the Patents Court. To no-one's surprise, it then went to the Court of Appeal which, for rather strange reasons, reversed the decision of the Patents Court. Everyone took it for granted that the case would now go to the House of Lords. Unfortunately, by this time their Lordships had had enough and leave to appeal was refused; so World War 3 ended before it had been given a fair chance to break the records set by its predecessors.

The main question that I want to explore this evening is why it was that such a large part of the pharmaceutical industry became almost simultaneously convulsed with patent litigation on this truly heroic scale. No doubt in each case there was good reason for the fight. However, the phenomenon was much too widespread through the industry to be dismissed simply as mere coincidence. Some might be inclined to look for a sinister explanation. The pharmaceutical industry gets a bad press these days and if, as some newspapers assure us, all pharmaceutical companies are greedy and heartless, it might be suggested that these terrific fights are just the sort of behaviour one would expect from greedy heartless warlords. However, members of our professions have good reason to know that what the newspapers print is not always either sensible or fair and it is, I think, worthwhile looking for a less superficial explanation.

In order to do this, it is necessary to consider a little medical history. If one goes back to the seventeenth century, both the pattern of disease and the pattern of its treatment were very different from the patterns today. The major diseases were the great epidemic infectious diseases such as plague, smallpox and typhus. Recurrent epidemics of these diseases swept regularly through various parts of Europe and the medical profession was largely incapable of dealing with them. The diseases were horrifyingly swift in their onset and generally ran

their course within a few days. In layman's terms, the question was whether the invading organisms would kill the patient before the patient's immune system had had time to respond to and kill the invading organisms. All that any doctor could do was see that the patient was properly nursed. If a smallpox patient was lucky, his doctor would prescribe nourishing food, light, air, and good nursing. If the patient was unlucky, his doctor would prescribe starvation, darkness, closed windows and frequent blood-letting. Thus the cure often killed off patients who might otherwise have had the strength to survive the disease. The more enlightened treatment, which amounted to little more than the application of commonsense, was pioneered by Dr. Radcliffe, the most fashionable physician of his day and a great benefactor of the University of Oxford. Physicians at Cambridge were apparently less enlightened. When the young Marquis of Blandford was taken ill of the smallpox at Cambridge he was bled almost to death. In desperation, his mother sent for Dr. Radcliffe. Radcliffe was never one to mince words about a rival. Having heard the treatment that the Marquis had been given, he refused to assist, "Madam, I should only put you to a great expense to no purpose, for you have nothing to do for his Lordship now, but to send down an undertaker, to take care of his funeral: for I can assure your Grace, he is dead by this time of a distemper called THE DOCTOR, that would have recovered from the smallpox, without the intervention of that unfortunate malady."

The apothecaries, the fore-runners of the modern pharmaceutical industry, were almost as dangerous as the doctors. Most of their recipes consisted of a mixture of things which could have no conceivable effect on the progress of the disease, together with the occasional substance that might help. However there was unfortunately sometimes an admixture of something potentially disastrous. I have chosen a few examples from Smith's *Complete Housewife* (1742) to illustrate the point. This is no doubt a later and a humbler work than some of the pharmacopoeias of the seventeenth century but it will serve to give the flavour of the remedies of the time:

> For any man or beast bitten by a mad dog. Take sage-leaves and rue, of each a good handfull, two or three heads of garlic, four pennyworth of the best treacle, a handfull of the smallest shavings of tin or pewter; boil all these in a quart of strong ale in a pipkin or stone crock, close stopt and pasted over, and set it to boil in a kettle of hot water, and put it over the fire for two hours; . . . give or rather pour it into the party bitten by five or six spoonfulls at a time, according to the strength of the party bitten, whether it be man or dog or other creature this must be given three days before the full or new-moon next happening after the party has been bitten.

The remedies for consumption are hardly more encouraging. One begins, "Take an old red cock from a barn-door . . .". Another, optimistically entitled "an Infallible Cure for the galloping consumption", begins mildly enough with "Take half a pound of raisins . . ." but ends rather glumly ". . . and if this will not cure you, the Lord have mercy upon you."

Not all the recipes are as hopeless as this. One, for instance, recommends the treatment of toothache with opium, then as now a good analgesic. In another, the author recommends the use of a mercurial ointment for treating venereal disease adding, fascinatingly,

> There are some hundreds of gentlemen in England, that can, from their own experience, bear witness to the excellency and efficacy of it; I myself, and three others that are now in company with me, have been all cured by it . . .

However, although some of these recipes might have done some good, three things are notable about them. In the first place, they are generally at best directed to treating the symptoms rather than the underlying disease. In the second place, where animal and vegetable substances are used there is almost no attempt to isolate the active ingredient. In the third place, there is no trace whatever of any of the chemical modification of naturally occurring substances which, as I shall explain presently, forms such an important part of modern pharmaceutical practice.

Fortunately, it is a happy fact of life that most people recover from most diseases provided that the treatment itself does not kill them! Furthermore, some of the remedies known at the time were of very considerable assistance. Thus, it was perfectly possible for apothecaries in the seventeenth and eighteenth centuries despite the limited knowledge of the time to prosper and grow in reputation. Dr. Radcliffe's apothecary was said to have been worth forty thousand pounds, an enormous fortune in those days. Furthermore, the general health of the population undoubtedly improved over the years. The recurrent epidemics became less frequent and less severe. This was largely because a rising standard of living made their transmission less likely; the rats and lice that carried typhus and the rats and fleas that carried bubonic plague were reduced in numbers. The cramped conditions and poor sanitation which favoured the spread of tuberculosis, typhoid and cholera were progressively eliminated. Furthermore, the discovery of vaccination meant that for the first time preventative measures could be taken against certain diseases. Finally, the population as a whole developed resistance to certain diseases and the attacks became less lethal.

All these developments could fairly encourage a spirit of optimism. However, the striking thing is that right up until the end of the last century the major developments had almost nothing to do with the pharmaceutical industry. At best, some of the useless or dangerous recipes were eliminated from the pharmacopoeia and some known substances, such as chloroform, were shown to have useful properties and so were added to it. But there was almost no synthesis of new chemical compounds for pharmaceutical purposes. It is true that there were some attempts. For instance, morphine had been isolated from the juice of the opium poppy in the early part of the nineteenth century and had proved to be an excellent analgesic. Towards the end of the century, it was modified chemically to make diacetyl morphine which at first seemed to be an even better analgesic and indeed, was thought to possess such heroic properties that it was optimistically named heroin. It was only afterwards that its dangerous propensities were discovered but by this time the name heroin had stuck and it still exists to remind us of one of the pharmaceutical industry's early miscalculations. A happier example was the conversion of salycilic acid, which was derived from willow bark and was known to have some value for the relief of pain, to acetyl salycilic acid, now known to everyone as aspirin. However, these were examples of relatively minor chemical modifications to substances that were already known.

The outstanding feature of the research-based sector of the modern pharmaceutical industry is that it has become much more adventurous chemically. Instead of confining itself to known substances and relatively trivial modifications of them which were tried on a hit-and-miss basis, it has produced new chemical molecules which are, as it were, tailor-made for quite specific purposes. To this end chemists, microbiologists, pathologists and so forth have worked together in teams to discover what parts of a molecule have what effect and to synthesize the most desirable molecule to achieve a specific function. It may be necessary to make thousands of different molecules before the right ones are discovered. There may be many false trails. But the end is to achieve pharmaceutical products which are much more specific in their action than their predecessors and much more directed to treating the underlying disease.

An example which may help to make the matter clearer and which, as it happens, has provided the most fertile area for pharmaceutical litigation, is that of the antibiotics. Antibiotics are substances produced by certain micro-organisms which have the capacity to kill other micro-organisms. Of course substances which will kill bacteria have been known for a long time. Such antiseptics as

carbolic acid were good examples. They were useful for sterilising utensils and could even be used to some extent for the dressing of wounds. However, once the infection had spread through the patient they were of substantially no use at all. It is true that if administered systemically they would probably kill the bacteria, but before doing so they would undoubtedly kill the patient. Certain antibiotics had the remarkable property that although lethal to the bacteria they had very low toxicity to human beings. It was thus possible to inject them directly into the blood stream and there they would in favourable circumstances eliminate the infection without harming the patient. The importance of this development can hardly be exaggerated. It meant that some infections which hitherto could have been treated only by, for instance, amputating a limb could now be dealt with chemically. The significance of this fact in treating persons wounded in war will be obvious. Less obviously but equally importantly, it meant that a large number of surgical procedures which hitherto would have been quite impossible because of a very high fatality rate from sepsis now became possible and, in some cases, almost routine. These include practically all major abdominal, brain and chest surgery. Thus the antibiotics not only made it possible to cure some hitherto incurable infections but also paved the way for surgical treatment of a number of conditions which would simply have been untreatable fifty or sixty years before. It is small wonder that in the 1940s some of the newer drugs were regarded as truly "miracle" drugs.

The original antibiotics, such as the original penicillin, were naturally occurring substances. The next step was the discovery that, while nature had provided these substances, it was possible for the chemist's art to improve on nature by modifying naturally occurring antibiotics to make wholly new substances. Some of these new substances had even more useful properties. Thus, while naturally occurring penicillins were effective against a certain range of bacteria it was possible to modify the penicillins chemically to make them effective against a much wider range of bacteria and thus to treat a much wider range of infections. Next, while naturally occurring penicillins are largely broken down in the digestive tract and therefore have to be administered by injection, it was possible to develop substances which could be taken by mouth and which were nevertheless well absorbed into the blood stream. Finally, as part of a continuing battle, it was possible to improve the efficacy of penicillins against the chemical weapons used by bacteria to break down the penicillins and so render them harmless. Thus succeeding generations of penicillins have become increasingly effective.

Corresponding developments occurred with other drugs. These developments were not easy. Once you move from a relatively limited range of naturally occurring pharmaceutically useful substances the possibilities for chemical modification are almost endless. Only a tiny proportion of these are clinically useful. Thus the pharmaceutical industry after the Second World War embarked on a massive programme of synthesising and testing new chemical substances. This occurred not only with antibiotics but over a vast range of drugs. The problems to be overcome were enormous. For instance, one might discover by elaborate searching a group of chemical substances which had some useful effect, such as a capacity for killing bacteria. But this is only the very first step towards finding a clinically useful drug. It is next necessary to show that the drug is not toxic towards humans and, much more difficult, that it has no unwanted side effects. The testing goes through several stages. Naturally if the substance under test is completely new, you cannot begin by administering it directly to humans. It is first necessary to perform elaborate screening tests on various laboratory animals. If small animals show no ill effects, one goes to larger animals and then on to human volunteers. But even this is not the end of the story. Even if the toxicity is low and there are no significant side-effects, the drug is still no good if it is intended to be taken by mouth and is broken down in the digestive tract or not properly absorbed into the blood stream. Even if it gets safely into the blood stream it may be no use if it is broken down in the liver or excreted too rapidly or if for any other reason it does not get to the site of the infection. The result is that typically tens of thousands of drugs must be synthesised and then tested to varying degrees before even one is found which is suitable for clinical use. The process typically takes many years and costs enormous sums of money.

However, while it might cost millions of dollars to identify which of thousands of chemical substances has the capacity to make a useful clinical drug, once you have identified the useful one it may be relatively cheap and easy to manufacture. However, it is obviously necessary for the pharmaceutical company which developed the drug to set a price which will properly reimburse it for the risks that it has taken and the expenses that it has incurred as well as the cost of manufacture. A rival company would suffer no such limitation. Once it knew *which* chemical substance was clinically useful, it might well be able to synthesise it and sell it at a price far below that which would be charged by the company that developed the drug in the first place.

It is in this context that patent protection has become so important in the pharmaceutical industry, because it is precisely this sort of pro-

blem that patent law is intended to overcome. Here at last, with apologies to the lawyers present, I can return to the law. The basic theory behind patent law is simple and elegant. An inventor, in return for disclosing his invention to the public, is granted a patent. During the sixteen-year term of the patent he has monopoly of that invention. He thus has a period of time during which he can develop and sell his invention. If the invention is good and sells well, he will make large profits; if it is poor and sells badly he will not. Thus his reward is in a sense proportionate to the value of the invention to the public. Nor are other manufacturers put at any unfair disadvantage. Although the inventor is granted a monopoly, it is a monopoly of a very special kind since he is entitled to monopolise only what is invented by him and is new; other manufacturers are perfectly free to go on making all the things that they made before he applied for his patent. This is of course in sharp contrast with most other monopolies, such as in land or commodities, in which what is monopolised is something that has already been present in the community. In patent law whatever was there before is still available to all. The next advantage of the system is that since the patentee enjoys his monopoly for only a fixed term he is given every possible incentive to put it on the market and thus make it available to the public as soon as possible. Finally, when the period of monopoly is over, the invention is freely open to all other manufacturers to use and so becomes part of the available stock of techniques or things open to everyone in the trade. In this way, the system both encourages invention and assists with the spread of technology from the inventor to the rest of the trade. In principle it thus keeps everyone happy.

It will be seen that if a pharmaceutical company is to engage in innovation, patent protection is absolutely essential. It is only by having such protection that a company which has borne the enormous expense of discovering a useful pharmaceutical product can enjoy the fruits of its invention without being undercut by its rivals. A corollary of this is that a successful pharmaceutical patent is one of the most valuable pieces of industrial property in existence. However, pharmaceutical research was by no means an automatic road to riches. By the mid 1960s most research-based pharmaceutical companies were in substance engaged in a vast financial gamble. If they ventured the enormous sums required to discover and develop a useful drug, they might or might not find such a drug and that drug might or might not be a commercial success. It was always possible, and indeed frequently happened, that an entire project would yield no useful drug at all. It sometimes happened also that a useful drug would be found but that meanwhile a rival manufacturer had found a better one. Now in

many areas of commerce it is possible for an entrepreneur to spread his risks over a sufficiently large number of projects to be confident that on average they will yield him a satisfactory return. By the mid 1960s this seems to have been no longer possible in the pharmaceutical industry. Even the most successful pharmaceutical companies generally had at most only two or three important patented drugs on the market. The less successful might have one and there were also some whose researches had yielded no useful drug at all. For the successful the rewards were very high, for the unsuccessful the gamble had simply failed. It is small wonder that the pattern developed and has continued, of pharmaceutical companies rising to prominence on the profits of one or two inventions and falling again when the patents for those inventions expired, unless they had in the meantime discovered something new to put in their place.

The high rewards for success and the disastrous consequences of failure ensured that there were by the mid 1960s a few highly profitable research-based pharmaceutical companies and that these were watched with varying degrees of envy by the less successful. This was fertile ground for litigation to commence. Here I return to the point at which I started in my search for an explanation of the orgy of patent litigation which broke out in the pharmaceutical industry in the mid 1960s. It was about then, that the change in the pattern of the industry to being much more experimental and research-based was bearing fruit. Thus companies were relying increasingly on patent protection in order to recoup their expenditure and rivals were looking to the easy pickings which would be available if they could sell the newly invented drugs without having themselves to bear any part of the costs of discovery and development. Certain areas became highly competitive and disputes about whether a new drug did or did not fall within an existing patent monopoly or whether a new drug was itself patentable became common. There were also bitter disputes between some English patentees and companies that wished to import substances patented in England but produced much more cheaply abroad. In saying this I am not suggesting that the patentees were always right. Sometimes they were altogether too greedy. However, I think that the very unusual and highly unstable state of affairs which had been brought about in the pharmaceutical industry goes far to explain the outbreak of litigation. Contrary to popular belief, manufacturing companies do not ordinarily resort to law to settle their commercial differences. But the circumstances here were so highly charged that there was no other way. On the whole, the law settled the disputes reasonably satisfactorily if by no means expeditiously.

The sequel was much less satisfactory and it is to this that I now turn. I have pointed out that by the mid 1960s the research-based sector of the pharmaceutical industry had become engaged in a vast financial gamble. While one suspects that many companies ultimately regretted entering the area at all, the gamble was probably worth taking so long as the chances of success were not too remote and the rewards of success were sufficiently high. The important thing to remember in following through the subsequent impact of the law on the pharmaceutical industry is that with time, the odds against success became longer and the rewards of success became smaller. There are, I think, basically two reasons why this happened. In the first place, the problem of developing new drugs became increasingly difficult. As any historian of science will tell you, this is by no means an uncommon phenomenon. In many sciences the first few steps are relatively easy to take and the results of taking them are absolutely sensational. After that, the science embarks on a period of consolidation during which successive steps require more and more man-years to achieve and the results become less and less sensational. While it is much too soon to say that this is happening on a substantial scale in the pharmaceutical industry, some of the signs are there. In a way, the discovery of penicillin amounted to too much success too soon. Penicillin was a quite abnormally good drug with an extraordinarily wide application and an extraordinarily low toxicity. It is by no means certain that one can go on discovering drugs that are as good as this. Furthermore, many of the drugs developed in the 1940s and 1950s were seen as life-saving drugs to be used only in emergencies. They were not developed as drugs which would be safe when used quite indiscriminately. As time has gone on, the industry has tackled the task of developing drugs which can be used by a much larger part of the population over a much longer period. In these circumstances, even very uncommon side effects can achieve a major significance. Side effects which are tolerated when life is at stake will not be tolerated where the drug is used on more minor occasions. Consider, for instance, oral contraceptives. These are taken by millions of women every day. The potential scope for side effects is obviously enormous. Viewed in this light, the extraordinary safety of oral contraceptives is, I think, one of the great triumphs of the pharmaceutical industry. It would, however, be quite wrong to assume that this degree of safety can be achieved in other areas. For all these reasons, I think that the tasks undertaken by the pharmaceutical industry were not only intrinsically difficult but in fact they became increasingly more difficult as time went by.

The other factor which helped to tilt the balance against the pharmaceutical industry was a change in public attitude which became perceptible during the 1960s and increasingly strong in the 1970s. Instead of the industry being regarded as a purveyor of miracle drugs, it came to be looked on with an odd mixture of optimism and distrust. The optimism derived from an earlier era. The public tended to treat miracle drugs as being the norm. It sometimes even seemed to go so far as to regard almost all medical problems as being capable of solution by pharmaceutical means and to show a slightly puzzled resentment that some problems had still not been solved. It was thus an odd survival of the optimism which has long since departed from the public perception of both economics and politics.

The distrust of the pharmaceutical industry became even more widespread. The industry became regarded as combining the more anti-social characteristics of Frankenstein and Dr. Strangelove, as playing with life and death and as showing a sort of manic destructiveness in so doing! Part of the distrust came, I think, from the understandable if not wholly admirable envy that is felt these days for anyone who makes large profits. It is rationalised by saying that such people must surely be up to no good. Silly politicians would refer, in the ugly idiom of their trade, to "the great Valium rip-off". The top companies in the pharmaceutical industry did make large profits in the 1960s and it came to be believed that this was true of all pharmaceutical companies. Furthermore the belief persisted even when, as I shall explain presently, the profits of the industry started to fall off rapidly. Public opinion is often behind the times.

However, the envy felt for an industry that was seen to be successful was reinforced by fears that some pharmaceutical products were simply not safe to use. These fears were vastly increased in the wake of the Thalidomide catastrophe. You will recall that Thalidomide was a widely prescribed drug which turned out to be teratogenic, a word derived from the Greek and meaning "monster producing". The unfortunate children affected by it were not monsters, but their limbs were imperfectly formed and they were consequently severely handicapped. The consequences of this were very far reaching as I shall explain in a moment. Governments the world over have taken precautions to ensure that drugs are safe before permission is given to market them. Pharmaceutical companies have also, of course, carried out vast programmes of testing for the same purpose. During the 1960s and 1970s, government requirements became increasingly stringent, particularly after Thalidomide. More important, the requirements became vastly more time consuming. In

the early 1960s, it seems that drugs could often be got onto the Australian market within a year or two of their discovery. As time went on an increasing range of obstacles was put before any company that wished to market a new drug. The applications themselves had to become enormous multi-volume documents. The range of questions asked and further experiments required increased. Above all, the machinery of the examination itself moved increasingly slowly. It became necessary to have specialists whose sole business in life was to prepare and prosecute pharmaceutical marketing applications. In Australia, the problem was of added complexity because of the range of Commonwealth and State authorities that must be satisfied before marketing proceeds. To an outsider, watching the progress of a marketing application is like entering the City of the Living Dead! There always seems to be one more committee that has to meet and consider the application and it always seems that its next meeting is months away. In this way, weeks lengthen into months and months lengthen into years. There have been several cases before the Courts recently in which it has taken more than ten years between the discovery and marketing of a drug.

These delays are of absolutely crucial significance to the patentee. Because his invention must be new when the application is filed, it is usual to lodge patent applications for pharmaceutical inventions as soon as some appropriate biological activity has been discovered. The sixteen-year term of a patent runs from the date of lodging the application. Thus the moment the application is lodged, time starts to run. If only a year or so is lost between application and marketing, the patentee still gets most of the benefit of his invention. But if ten years or more go by, then for most of the sixteen-year term one part of the law has given him a monopoly, which another part of the law does not allow him to exploit. The law gives and the law takes away and the position from the point of view of the patentee is highly unsatisfactory.

Sometimes, the position is even worse than I have suggested. There have been cases in which a drug is not finally got onto the Australian market until the term of the patent has almost expired. Thus the patentee loses almost the whole of the advantage of his patent. Fortunately, the Act provides some remedy for this. It is possible for a patentee to present a Petition to the Supreme Court asking for an extension of the term of his patent on the ground that he has been inadequately remunerated. However, the range of issues that the Court has to consider is unfortunately so large that the preparation and presentation of such a Petition is in itself a very costly exercise. Thus, while there have been some Petitions heard and exten-

sions granted in recent years, they have been mainly concerned with major inventions where the likely reward from an extension of term is sufficient to justify the cost and uncertainty of presenting a Petition. Where a drug has a smaller potential market, it is simply not worth proceeding.

In the present climate of public opinion, these difficulties are likely to attract little sympathy. It may be said that the pharmaceutical companies themselves embark on a gamble and that what has been happening recently is simply that in an increasing number of cases the gamble has not paid off. That, it may be said, is a common fate of gamblers. The difficulty with this view is that we are not concerned simply with those who frequent race tracks or casinos with a view to a little excitement. We are concerned with large public companies who, in order to develop a new drug must invest millions of dollars. While the actual inventions may be made by dedicated scientists, the financial control of such companies is almost certainly vested in accountants. And if the accountants and their doleful brothers the actuaries, see that the odds against success have become too long and the rewards of success have become too small, they will be tempted to pull out of the operation altogether. There are signs that this is beginning to happen. Pharmaceutical companies are moving increasingly towards selling non-proprietary standard drugs rather than towards developing new ones. Furthermore, those that remain research-based have tended to move towards safer areas like minor improvements on existing drugs rather than towards more adventurous projects. Finally, they have tended to move from difficult and not particularly lucrative areas like anti-cancer drugs towards areas in which the drugs can be sold on a mass market and the profits will be larger. What I have said, is, of course, a broad generalisation. But it is supported by individual instances known to me. I think that it is also supported by the overall trends now perceptible in the development of new drugs. They have been the minor improvements or the mass market drugs. All this has very serious implications for those patients who have the misfortune to suffer from relatively uncommon maladies. There is, I think, a real danger that the pharmaceutical industry is being squeezed world-wide away from the sort of brilliant invention which may be of tremendous importance to a small number of patients but which can never hope to meet a mass market. This is a trend which we allow to continue at our peril.

Even in the mass market drugs, there is, I think, a danger that the pharmaceutical industry is becoming less inventive than it was fifteen or twenty years ago. Of course, it might be said that this does not matter much as we already have good antibiotics, tranquillisers and

so forth and should just make do with these. That this is not true can, I think, be shown by considering the example of antibiotics. I have explained that some of these were initially regarded as miracle drugs and that there was indeed good reason for the high reputation that they enjoyed. However, the mere fact that an antibiotic was effective against the bacteria of the 1940s does not mean that it will similarly be effective against the bacteria of the 1980s. Unfortunately bacteria have their own way of coping with antibiotics. If they are constantly exposed to them, as they have now been over many years to the penicillins, resistant strains grow up. These strains, unlike their forbears, no longer respond to exposure to the drug. It is only by keeping up a supply of new drugs that one can be sure of eliminating all strains. During the 1960s there was available a wide range of antibiotics to which resistant strains had not yet built up. In subsequent years the growth of the phenomenon of resistance has been more rapid, as I see it, than the arrival of new antibiotics. Members of this society will have noticed the publicity which has recently been given in the press to a strain of staphylococcus aureus which seems to be resistant to practically all the antimicrobial agents which have been tried on it. At present it seems to be limited to a few hospitals and it may be said that it does not justify the alarm that has been expressed. But while this particular strain may be controllable, the phenomenon of resistance is a really worrying one and, as I see it, it can in the long run be beaten only if a new range of antimicrobial agents is developed every few years. Unfortunately there are few signs of major new antibiotics in the course of development.

Consequently, the world-wide pressures that have been put on the pharmaceutical industry are likely to drive it to being much less useful for the community in the future than it has been in the past. Furthermore, I do not think that it can be accepted without question that all the regulation which is at present imposed is valuable even for the limited aim of regulating the arrival of existing drugs on the Australian market. It is true, that by taking very stringent precautions one can achieve tolerable certainty that a new drug will not be harmful. However, if the new drug is in fact a valuable one then a delay of many years before it gets on the market will mean that a number of patients who could have benefited by it have lost that benefit. An example of this came before the Supreme Court a few years ago. A pharmaceutical company had developed a drug which was useful for treating a common and often fatal form of cancer. It was not, of course, a complete and miraculous cure but it offered patients who might otherwise have been very ill at least a year or two of more comfortable life without being handicapped by their disease and with

some possibility of ultimate remission. The drug has now become a treatment of first choice in many cases. However, the drug took more than fourteen years after its discovery before it got onto the Australian market other than by way of limited trials. There are between one and two thousand new patients per year in Australia who can benefit by it and so literally thousands of patients were deprived of what is now regarded as a treatment of first choice because of the legal delays of getting that drug on the market. In saying this, I am not suggesting for a moment that in that particular case there was blameworthy conduct. I am simply pointing out that mere regulation is not all good and can, although in a concealed fashion, cause real harm to many thousands of sick people.

More generally, I am by no means convinced that the present procedures could not be speeded up enormously or that it is necessary for a pharmaceutical company to prepare, as it is required to do, a range of documentation for marketing in Australia which is different from the documentation required in the United States and Great Britain. Neither of the two latter countries is known for carelessness towards the health of its citizens. There is much that can be done but, because the problem is concealed, the incentive is lacking. I think that the position that has been reached is, somewhat ironically, that in a world-wide search for greater safety the authorities in Western Countries taken collectively may be doing great harm to the health of the population both by preventing new and useful drugs from being discovered and from delaying the availability of those drugs to patients. I suspect further, that when the medical history of the present century comes to be reviewed, it will be seen that the major harm caused by Thalidomide was not that caused directly to the recognised victims. Rather that it induced an attitude in the authorities in which almost any delay was regarded as being tolerable in getting new drugs on the market in order to eliminate any perceived risk, however remote that risk might be! The damage done when a good drug is kept off the market is just as great as that when a bad drug is allowed onto the market. The former sort of damage is never perceived because one can never identify directly who the victims are. If we are not to have an increasing number of "hidden" Thalidomide victims, there is a real need for changes in the law and in public attitudes towards the pharmaceutical industry.