Drug research and development in the pharmaceutical industry

B. W. CROMIE

Hoechst UK Ltd, Hoechst, Hoechst House, Salisbury Road, Hounslow, Middlesex TW4 6JH

Introduction

Innovative research is the back-bone of the pharmaceutical industry and has been the basis of most of the improvements in clinical care over the last 30 years. The U.K. industry has been singularly successful and those past triumphs will be documented by others in this symposium. However, yesterday's miracle becomes today's routine. That has happened with all technical innovations from the telephone, the radio and the ball-point pen to the calculator and the video-recorder. It has certainly occurred with medicines and a generation of doctors and patients has grown up, which accepts improved medicines as the norm rather than as therapeutic wonders. Things which are casually accepted in this way are not appreciated and not fought for. They can slip away and nobody worries until it is too late.

Pharmaceutical research which has been so successful, particularly in the UK where twelve out of the top twenty of today's medicines were invented and developed, may be at risk and we must play our part if we want miracles tomorrow as well as yesterday. Pharmaceutical research really got going in the 1950s and blossomed in the 1960s and early 1970s but is already showing signs of decay.

The investment in research in the US in terms of units of real research being bought is declining (Figure 1) (Pharmaceutical Manufacturers Association, 1983) and senior Wall Street analysts have said '... there is no cause for optimism by investors.' (IMS Pharmaceutical Market letter, 1984) and 'major drug companies face a rocky road, due to plateauing pharmaceutical innovation, loss of pricing flexibility and the like' (Scrip, 1984).

In the UK, the research expenditure is increasing but only marginally in real money values (Figure 2) (Association of the British Pharmaceutical Industry Annual Report 1984) and is certainly also decreasing under the US concept of taking into account the research effort purchased. Apart from the probable decrease in investment, there is no doubt about the decrease of new chemical entity introductions world-wide

(Figure 3) (Office of Health Economics, 1983). If the decline in stimulus for R & D continues and the trend of decreasing innovation goes on, it is quite possible that the burst of successful research will pass, as it already seems to be following a cyclical path which will approximate to zero around the end of the century.

There are many reasons for this adverse trend but I would like to concentrate on two, which are having a major effect on UK: R & D and which could be reversed if there was public awareness and political will.

Patent erosion

The Banks Committee report (HMSO, 1970), published in July 1970 stated 'we believe the community stands to benefit greatly from the discovery of new drugs. We also tend to the view that the discovery and development of new drugs is becoming an increasingly difficult task, and that the full protection of the patent system will be necessary to provide sufficient stimulus to innovation in this field.'

At that time, the average interval between filing a patent for a possible new medicine and obtaining a product licence so that it could be made available for prescribing in the UK was 6-7 years; giving an effective patent life for monopoly sale of 9-10 years.

This effective patent life of 9-10 years was based on a total patent life of 16 years but, largely as a result of the Banks report, the 1977 Patent Act increased patent life for all new products, including medicines, to 20 years. This became effective in June 1978, so that patents for new medicines filed after that date were given a 20 year patent life (for example, a potential new medicine filed in September 1978 is likely to get a product licence in about 1992 and have an effective patent life of 6 years or less before the patent expires in September 1998).

Medicines which had existing patents on 1st June 1978 were either granted or were able to claim an extra 4 years of patent life but all had Licence of Right endorsements, so

Figure 1 US pharmaceutical R & D expenditures as a percentage of pharmaceutical sales, 1965–1982*

* R & D as a percentage of sales is computed by dividing human and veterinary R & D expenditures in the US by domestic production, i.e., domestic sales and exports, including intra-firm transaction, $\times 100$.

** Sales deflator: producer price index for Ethical Pharmaceuticals, Bureau of Labor Statistics: 1967 = 100.

R & D deflator: biomedical R & D deflator used by the National Institutes of Health, Department of Health and Human Services: 1967 = 100. (From the Pharmaceutical Manufacturers Association, 1983).

Figure 2 UK pharmaceutical R & D expenditure; ■, 1953 prices; □, current prices (from ABPI annual Report, 1983–84).

Figure 3 World-wide introduction of NCEs; ----, 3 year moving average; —, total NCEs (From OHE, 1983).

that their protection against copyists was incomplete.

A detailed study of all New Chemical Entities (NCEs) introduced into the UK in the last 23 years (Walker & Prentis, 1985). Figure 4 shows clearly that the limited extension recommended by Banks had already been overtaken by increased drug development work by the time that the new 1977 Patent Act was in force.

Despite marginal improvements, such as the introduction of the CTX (Clinical Trial Exemption) scheme, the trend of an ever increasing time between filing of patents and obtaining a product licence was already in evidence. By the time the 1977 Patent Act is fully operative in 1998, the average residual effective patent life will be of the order of 2·3 years.

It has been estimated that it currently takes 19 years of world-wide sales to recover R & D investment (Grabowski, 1982) and, with rapidly increasing generic prescribing, full world-wide sales are more and more dependent on patent life. Thus the high risk of investment in pharmaceutical research becomes impossible and explains the trend away from such investments, referred to above.

Quite apart from this unrealistic commercial risk, any pressure to get later patents or earlier product licenses in order to have a longer effective patent life, cannot be in the interests of science or of patients who depend on maximum toxicity and safety testing in an unhurried way.

I believe that I have presented a likely forecast but the eventual demise of pharmaceutical R & D in the UK is not inevitable.

There is some recognition within Government that the most successful of their high-tech industries could be in jeopardy and a recent Green Paper (HMSO, 1983b) gives a hint that the door for change is not slammed shut. It states: 'Conversely for those products which are delayed from entering the market by lengthy Government regulatory procedures, the period of patent monopoly might be extended to compensate.' In addition, the US Senate has just passed a rather messy bill but it does give up to 5 years extra patent life and a minimum of 10 years patent protection for recently approved medicines. It is understood that similar legislation in Japan is probable.

These moves in the US (and Japan) could well provide the stimulus for the UK and other

Figure 4 The erosion of effective patent life 1960–1982 (modified from Walker & Prentis, 1985)

European countries to amend their own patent laws in advance of a change in the European Patent Convention. Nobody is suggesting that it will be simple to restore pharmaceutical patents but it can certainly be achieved with public pressure and political will.

Animal experimentation

The use of animals in pharmaceutical research is very costly, less than predictable and ethically unpleasant for the research workers involved. Accordingly, no individual scientist or research laboratory would use one more animal than necessary and would always use alternative methods, if they were available, reliable and acceptable to the regulatory authorities.

Basically, research workers are in line with all animal lovers who want research for new medicines and standardisation of insulin and vaccines to continue but using the minimum number of animals and subjecting them to the least possible degree of stress. That much is common ground and is also the basic philosophy of the recent Government White Paper (HMSO, 1983a) on Scientific Procedures on Living Animals. This states 'The Government has a duty to safeguard the community from avoidable harm—and indeed tragedy—and to enable science to continue to make progress in saving lives and alleviating suffering. This duty obliges us to permit

the use of animals in research and testing to continue.'

One suspects that the vast majority of the population would also agree with this line if the whole subject was explained to them in a balanced way, capable of being understood. Unfortunately, the people able to give such a balanced explanation are generally silent or defensive or afraid or not given the opportunity to make their views heard. This leaves the field clear for minority groups who have extreme and unrealistic anti-research views and their voices are certainly heard. They place advertisements, they run meetings, they mount campaigns, they are expert at getting media coverage with vigils and demonstrations but they also act illegally against research activities.

These activities include raids on laboratories, personal attacks on research workers and harassment of their families. Apart from well publicized raids by guerilla-type groups and the daubing of paint on well-known scientists, there have been personalized demonstrations around one industrial toxicologist as he came out of church with his family and very many calls to the homes of research workers with the words 'Do you know your Daddy is a murderer?' when a child answers the telephone. With such methods, the anti-vivisection publicists seem to have won the hearts and minds of the average man. He no longer asks about the need for research but has been brain-washed to feel that

animal experimentation is bad under all circumstances.

An anti-research, anti-researcher environment has been created in this country which is a definite deterrent to young people looking for careers and is a long-term threat to good R & D in this country.

In addition, the anti-research atmosphere is already evident in the mail-bags of M.P.s and could well influence the final version of the proposed bill on *Scientific procedures on living animals*.

This could place the UK at a disadvantage for research, compared with other countries and be a factor in relocating pharmaceutical R & D elsewhere. Can this be changed before it is too late? I have no doubt that all involved in R & D will do their part but are seen as biased, interested parties and accordingly ignored. What is needed is a respectable and reputable establishment body that has the interests of animals at heart but recognizes the need for continuing research to speak out. They should speak on their own initiative but certainly at times of animal-liberation publicity. You may ask, as I did, is not the Royal Society for the Prevention of Cruelty to Animals (RSPCA) just such an organization?

The RSPCA produces literature on the subject of animal experimentation (1985b).

The text states — the RSPCA '... is opposed in principle to *all* experiments or procedures which cause pain, suffering or distress', '... any experiment using animals is potentially capable of causing pain. .', 'We have to concede, however, that politically there is no possibility that animal experimentation will be stopped in the foreseeable future. With that proviso, the Society has outlined four priority areas in need of most urgent reform and is currently taking action.'

So the RSPCA is opposed in principle to virtually all animal experimentation. There is no concession on the benefits to animals and man from research, the need for public safety or the need to standardize vaccines and the like. There is a recognition that they cannot change the world today but the basic anti-R & D principle still stands.

Despite this, RSPCA is the respectable voice of animal welfare. According to their own statements (RSPCA, 1984a) 'the RSPCA had a top-level meeting with the Parliamentary Under-Secretary at the Home Office' and 'were invited

to submit further expert views . . .'. The Head of the RSPCA Animal Experimentation Research Department is stated as being 'a member of the Home Office Advisory Committee on Animal Experiments and is therefore able to put the animal welfare case at the very highest level within the Home Office'.

Presumably, the Home Office and the Ministers involved know the basic anti-R & D stance of the RSPCA and can interpret accordingly but I am certain that this is not appreciated by the man in the street. I do not believe that we can educate the public and alter the current anti-research mood which is so detrimental to the research-based industries while the apparently balanced establishment organization of the RSPCA supports its current view and gives a respectable umbrella to the militant and often illegal animal-liberation groups.

Part of any campaign to educate and inform on the need for animals in R & D must include an attempt to get the RSPCA to speak publicly on its attitude to research and the use of animals in standardization of vaccines, etc. It must be seen for what it is and placed firmly as an extreme group which does not represent the reasonable animal-lover who wants necessary R & D to continue.

Unless that happens, I fear that the anti-R & D atmosphere in the UK will increase to the detriment of pharmaceutical innovation.

Conclusion

I feel that the continued successful pharmaceutical research in the UK is under threat. I have tried to draw attention to two factors which contribute to this threat.

I have, in the past, been called a pessimist and the Cassandra of the industry, in particular in 1978, when I spoke of the potentially disastrous trend of increasing time between patent and product licences (Cromie, 1979). One pharmacist leapt up from the audience to say that the trend was ridiculous and would soon improve. Well, 6 years later, I look at the criticized trend and update it. I regret to say that my pessimism was justified (Figure 5) (Cromie, 1979).

As Lawrence (1983) stated 'We must respond to real risk, not perception of risk' and I submit that the two factors described today are real risks, which require a response.

Figure 5 Time lag between first publication and marketing of NCEs.

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