parties do not have a parliamentary majority and would therefore be unable to enact the measures the people had voted for. This would probably lead, sooner or later, to a government crisis and new elections.

While the different factions squabble, the Swedish Council for Planning and Coordination of Research is trying to produce impartial, informative material. It has engaged pairs of authors with different opinions on energy questions to argue their cases on eleven topics, including how to store nuclear waste, how to heat houses, nuclear power and nuclear weapons, and sun, wind and biomass. Each of the pairs has a mediator whose task it is to clarify where the authors agree and disagree.

Whatever the outcome of the referendum, the campaign has demonstrated a lot about the treatment of a complex scientific and technical issue in a democracy. Rational argument about energy has been relatively unimportant. What has been important is politics.

Supporters of option three oppose nuclear power largely, it seems, because they see it as a symbol of many unattractive features of modern, post-industrial life: individual isolation, large-scale technology, powerlessness of the individual to determine living conditions, and so on.

Supporters of options one and two talk about the waste of investment if the country does not use reactors it has built. What they envisage is essentially a continuation of Sweden's post-war history: an economically-expanding society using the latest technology to secure personal welfare. □

THE Swedes estimate that the International Nuclear Fuel Cycle Evaluation (INFCE) has increased their chances of obtaining United States approval for reprocessing spent fuel from their reactors. Because they use American enrichment facilities, they are currently forbidden to reprocess spent fuel under the US Nuclear Non-Proliferation Act of 1978.

After the INFCE discussions, however, the US may well give Sweden permission — however guarded — to send spent fuel to existing reprocessing plants and leave the plutonium there.

All Swedish decisions on nuclear matters are in abeyance at the moment, pending the referendum. Irrespective of the result, however, nuclear policy will probably develop along the lines of rejecting a national facility for reprocessing and not insisting on having the plutonium processed abroad sent back. Sweden might well sell its plutonium to the countries which reprocessed it. Such a development would dovetail nicely with some sort of American permission to reprocess.

The two countries are negotiating a new agreement on nuclear cooperation, and it will be as part of this agreement that the reprocessing question will be raised.

Drug innovation— what's slowing it down?

The research and introduction of new drugs has been slowing down in the UK and the US. At the same time, government regulations on the safety of new drugs have increased. But **Fred Steward** and **George Wibberley** argue that there is not a simple relationship between these two trends

THE INFLUENCE of government safety and efficacy regulations on pharmaceutical innovation has become a prominent issue in relations between the industry and the British government. Last April the Association of the British Pharmaceutical Industry (ABPI), in its "election manifesto", criticised the government for producing "a cumbersome and expensive regulatory edifice, much of which serves little useful purpose so far as the well-being of the public is concerned". Vice-President Dr Peter Main singled out as a fundamental concern "the effect that the ever-increasing delay caused by regulations relating to the testing of new products was having on pharmaceutical research and innovation". The Association's news sheet has continued to give emphasis to the issue, accompanied by headlines such as 'Murder by Regulation' and 'Take off the Cuffs'.

Last September the new UK Health Secretary, Mr Patrick Jenkin expressed his concern that controls for reasons of safety, quality and efficacy "can reach a point where they are so thorough, so pervasive and so foolproof that everything comes to a full stop". He was anxious that "unnecessary impediments to innovation should be removed".

These views on the drug industry have been accompanied by mounting pressure against government legislation by other sections of British industry, and they have been anticipated in many ways by apparently similar arguments in the United States. The recent federal review of industrial innovation attributed negative effects to laws concerning health, safety and the environment, a conclusion much in tune with President Carter's commitment to "reduce, rationalise and streamline the regulatory burden". Attention has been focused throughout the 1970s on the impact of such controls on the performance of the drug industry, culminating in the introduction of a variety of proposed drug regulatory reforms in

Congress during 1978 and 1979.

The time is therefore appropriate to ask what exactly are the effects of regulation on innovation in the drug industry? Two points need to be made at the outset: much of the data and analyses have looked primarily at the US situation; and there are factors other than the legal environment influencing drug innovation. The Pharmaceutical Innovation Group at Aston University has been gathering data on drug innovation in the UK with the aim of evaluating the influence of regulation compared to other factors.

The annual rate of introduction of brand-name pharmaceutical products which doctors in general practice can prescribe in the UK has declined substantially from 1960 to the mid-1970s (Fig 1). This includes duplicates, new formulations, dosages and combinations of existing drugs. New chemical entities (NCEs) — products containing a new chemical substance — comprise only a small proportion of all new products. The annual rate of introduction of NCEs into

Figure 1: pharmaceutical products introduced into the UK 1960-79

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the UK market also declined in this period from about 30-40 to 15-20 per year; this rate remained reasonably steady throughout the 1970s.

Similar trends have been observed elsewhere. An analysis by Erika Reis-Arndt of the annual rate of introduction of NCEs into the world market showed a decline, mainly in the late 1960s, from nearly 100 in 1963 to 65 in 1973. The rate of introduction of NCEs into the US market, according to the data of Paul de Haen, shows an even sharper drop, from over 70 in 1960 to less than 20 in the 1970s.

The general decline in the rate of introduction of new drugs in the 1960s coincided with the introduction of stricter requirements in the UK and the US for the pre-market testing of new drugs. In the US the 1962 Kefauver-Harris amendments asked for evidence of efficacy in addition to evidence of safety already needed under the 1938 Food, Drug and Cosmetic Act. In the UK, a system for evaluating drug safety was introduced after the thalidomide disaster. The non-statutory Committee on the Safety of Drugs chaired by Derrick Dunlop began operating in 1964 and was replaced by a statutory licensing system involving the Committee on the Safety of Medicines under the 1968 Medicines Act. This put emphasis on efficacy as well as safety.

There are two particular difficulties in assessing the relationship between these regulatory changes and shifts in the rate of innovation. The first is that the large size of the US market and the importance of the US industry means that domestic regulations affecting them may have wider international repercussions; and the second is the fundamental problem of separating the influence of regulatory and non-regulatory factors on the pattern of innovation.

If there is a need for government intervention to prevent the marketing of inadequate drugs, then as a consequence of established control mechanisms, a decline in the introduction of inadequate products would be expected.

The greatest decline in new drugs in the UK has been of those containing an active ingredient already available in some other product. In the past, the medical profession has criticised the proliferation of similar and unnecessary combination products. The Committee on the Review of Medicines recently emphasised their lack of therapeutic value. There have been few claims that innovation in the formulation of existing drugs has been inhibited in recent years. Instead, the decline in the introduction of products based on existing drugs appears to fulfil the explicit objectives of regulatory policy.

The fall in the rate of introduction of NCEs is more difficult to analyse. By definition they possess some chemical novelty, but this is no guarantee that they all offer benefits in terms of safety or effectiveness. In the US, the Office of

Figure 2: withdrawal of new chemical entities introduced in the UK 1960-75

Health Economics has obtained assessments by clinical experts of the therapeutic significance of NCEs introduced between 1958 and 1970.

Studying the introduction of NCEs in the UK, we found that the proportion in the bottom category of 'little or no advantage' dropped from 32% in 1960-63 to 18% in 1967-70. This included products which failed to meet the basic minimum standards set by the control system. Again, this decline appears to fulfil policy objectives. A classification by the Food and Drug Administration (FDA) of NCEs introduced in the US also showed a decline in the bottom category, representing 'no therapeutic gain', from 75% of 1961-1962 introductions to about 40% of introductions in the late 1960s and early 1970s.

It is remarkable that in the wide range of studies on regulation and innovation, relatively little effort has been devoted to exploring more thoroughly the degree to which the primary intended effects of regulatory change have been fulfilled. We have examined the rate of failure as shown by subsequent market withdrawal of NCEs introduced into the UK. The lack of attention given to this was illustrated early last year when the then Health Minister could not give any information in response to a parliamentary question about the extent of, or reasons for, the withdrawal of drugs from the UK market.

An NCE may be withdrawn for a number of reasons, including toxicity problems, inadequate efficacy and poor market performance. Our analysis of the withdrawal of NCEs introduced in the UK from 1960 to 1975 (Fig 2) shows a very much lower overall rate of withdrawal of NCEs introduced from 1964 onwards. Over 20% of the NCEs introduced in 1960-63, before the Committee on the Safety of Drugs started operation, were subsequently withdrawn from the market. Recent introductions may distort these

figures but the trend shown bears out the view that fewer drugs which ultimately failed reached the market after the establishment of stricter control.

The persistence of NCEs with unacceptable toxicity shows the importance of more effective surveillance of drugs when they enter medical practice. Some of the decline in the rate of introduction of NCEs in the UK therefore fulfils the goals of drug control policy.

The 1960s decline in the rate of NCE introduction, however, cannot be accounted for in this way. Increases in cost and length of time involved in discovering and marketing new drugs are also factors.

We measured the time from patent or publication, to the marketing of a new drug in the UK. Averaging about three years in the early 1960s, this rose to about 7.5 years in the early 1970s and remained then reasonably steady until a rise to nearly nine years in 1978-79. These increases have often been attributed to the demands of regulatory bodies, and it has been suggested that the overall decline in the rate of NCE introduction is a consequence of drug regulation.

But what are the other possible influences on the time and expense of drug research? A number can be suggested. The identification of many biologically important chemicals shortly after the war may have created a fruitful basis for innovation, for a period, but subsequently showed diminishing returns. Changes in the attention given to certain diseases could also have significant effects on the discovery and evaluation of new drugs. The complex aetiology of diseases such as cancer poses problems which cannot be resolved simply by expanding the screening of new compounds. The complexity of cardiovascular diseases again illustrates the difficulty of finding clear cut cures. There is, therefore, a need for more extensive evaluation of the effectiveness and toxicity of drugs intended for long-term administration.

Some of the areas in need of major innovation, such as inflammatory disease, raise the particular problem of suitable animal models for screening purposes. All these factors point to more complicated, time-consuming and expensive drug research. Another factor may be the rising expectation of researchers for more sophisticated and expensive equipment.

An analysis we have undertaken of the diseases for which new drugs are introduced in the UK shows a shift from infectious diseases in the mid-1960s to cardiovascular disease in the mid-1970s. Detailed information on pharmaceutical R&D in the UK is not readily available, but some figures have been published for the US by the Pharmaceutical Manufacturers Association. These show that in 1977 35.9% of total R&D expenditure was incurred by discovery-oriented work of synthesis, extraction, biological screening and pharmacological testing. Clinical

evaluation took 22.5%, toxicology and safety testing 9.2% and regulatory preparation and submission 3.3%.

Although the rate of introduction of NCEs stabilised during the 1970s, it is becoming harder to discover new molecules of real therapeutic importance. Of 83 NCEs approved by the FDA between 1974 and 1978, 62% were considered to offer moderate or important gains. This contrasts with only 33% of the 45 new molecules in pending new drug applications in March 1978.

Whatever the cause of increases in the cost and time of drug innovation, the consequence has been a decline in the "productivity" of R&D investment.

The influence of regulations in the US has received considerable attention, much of it concerned with different rates in the introduction of NCEs in other countries. William Wardell, in particular, has documented in detail a persistent "drug lag" in the US from 1963 onwards, shown by the high number of NCEs introduced in Britain but not marketed in the US, or only marketed there some years later.

Although the marketing strategy of a particular company determines the country in which the drug is introduced, many of the differences between the US and UK arise from differences in regulatory approach. There have been conflicts between the FDA and its critics over the therapeutic significance of the 'lag'. Some have argued that important new drugs such as sodium cromoglycate were excessively delayed while others have replied that the proliferation of very similar drugs, such as the non-steroidal anti-inflammatory drugs, has been avoided. Wardell has criticised the administration of the regulations and not the existence of the 1962 Amendments.

Perhaps an acknowledgement of all these points lies in the FDA's new fast-track approval process which allows important innovations to move more quickly through the regulatory system. The mean approval time for 'promising therapeutic advances' in the year beginning October 1978 was 19.4 months compared with an average of 39.2 months for those of 'little or no therapeutic gains'. But the speedier British system carries disadvantages. Of the four NCEs introduced in the UK since 1964 that were later withdrawn on the ground of unacceptable toxicity, three (ibunefac, practolol and alclofenac) were never introduced in the US.

Any comparison of the risks of adverse drug reactions with the risks of delay in the introduction of important new drugs, presents serious difficulties. The assumption that reduction in the risk of adverse effects from drugs must be accompanied by an increase in the time taken for their introduction is not necessarily valid. Labels for regulatory systems such as 'strict' or 'fast' should be used cautiously especially when comparing

one system with another.

The underlying weakness of many studies on the relationship between drug regulation and innovation is that they treat R&D as a "black box" and use highly aggregated measures of innovative output. Although correlations have been observed between factors such as regulatory change, development time, research costs, and the rate of innovation, they have not been accompanied by comprehensive explanations of what changes have been taking place within the research process.

The decline in R&D productivity has meant changes in strategy. The proportion of expenditure on "basic" as opposed to "applied" research in the US drug industry fell steadily over the decade 1968-78 from 15.4% to 11.4%. British data are not precise enough to detect such a trend. There also seems to have been a move away from less economically significant disease, such as those affecting small numbers of people, or those prevalent in poorer parts of the world. Our analysis of the introduction in the UK of drugs for uncommon illnesses as a proportion of all new drugs shows a drop from 7.1% in 1960 to 4.7% in 1971-76. These changes are taking place in the context of companies concentrating on fewer therapeutic areas. Jerome Schnee

has shown that those US drug firms which concentrated research on fewer areas produced an average of 1.3 NCEs in 1972-75 while those which diversified their research generated an average of only 0.67.

These changes in R&D strategy may have major social consequences. The shift from basic research may well result in just the opposite effect to the closer relationship between basic and applied science. Changes in the therapeutic categories receiving attention may mean a neglect of important breakthroughs in less commercially attractive areas. Although such research decisions have widespread repercussions, they are not subject to any direct form of social control. The proposition that less, rather than more, government intervention is required in relation to drug innovation is at least an arguable one.

The precise relationship between regulation and innovation has yet to be established, and it is unlikely to be determined by further studies which attempt to quantify the adverse effect of regulation but do not examine the full range of factors which may influence drug innovation. We are exploring research and innovation in the drug industry with this perspective in mind. □

Evaporation apparatus for concentrating drug solutions in use at the Wellcome Laboratory of Drug Metabolism, Beckenham, Kent, UK.