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Commentary
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Medicine Development Needs Radical Reform: Commentary

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Commentary

Medicines are a vital and an expensive component of health care. The present situation with regard both to the development and licensing of medicines, and to their pricing and supply are in a state that damages the provision of healthcare particularly in poorer countries but also throughout the world. There is surprisingly widespread agreement that the whole process requires radical reform. The political will to bring this about has, however, so far not been sufficient to effect more than rather minor changes.

There are a number of underlying causes

The first is the unachievable expectation that medicines should be entirely safe. Any compound that has any pharmacological activity is almost certainly never entirely safe. Depending on the diseases at which medicines are aimed, various degrees of toxicity are tolerated. Most anti-cancer medication is quite toxic and much is, in itself, carcinogenic in the long term. On the other hand, drugs that are used for relatively harmless conditions are required to have a much lower incidence of side effects and possible toxicity. It was the introduction of thalidomide as a treatment for morning sickness in pregnancy which is responsible for much of the ever increasing ratchet ting up of safety requirements that have done so much damage to medicine development [1,2].

The second underlying cause is the litigation culture-particularly in the United States – where anyone who has suffered side effects or harm following taking a medicine can claim compensation and where class actions, often for hundreds of millions of dollars, have been pursued even for drugs where no causal ill effect has even been legally established. For example AstraZeneca paid $198 million compensation for side effects from Seroquel in 2010 even though a court had found in their favour a few months earlier. Encouraging class action litigation in this way may perhaps be compared to paying ransoms to kidnappers. It may solve an immediate problem but encourages more of the same in the future. Companies should be liable for compensation only when they have been negligent or actively at fault. They should not be regarded as at fault for "statistically associated" side effects.

Medicines in the United States, and to some extent in Europe, are subject to strict liability rather than to the law of tort so that the liability of the supplier cannot be diminished even where patients give informed consent to using a drug that is known to have some hazards. In the United States, very large damages have been given to those who have suffered side effects. On the other hand, those who have suffered severe disease or died from a disease for which a drug might well have been available come outside any form of compensation. This distinction in law between harm due to commission, which carries liability, and harm due to omission, which usually carries none, is, in general application, controversial among philosophers but in the particular case of medical practice, doing nothing is just one option among many and there is arguably no justification at all for the distinction.

A solution that I have long advocated is to abolish the extremely expensive and time-consuming Phase 3 trials, initially on a trial basis, so that the new regimen can run in parallel with the current regimen. The new regimen would allow patients at the end of Phase 2 to elect to have the medicine after the benefits and potential dangers have been explained to them. This would have great advantages of halving both the development costs and the time from discovery to clinical release; and would also allow a larger number of smaller companies to take drugs to market. This is currently impossible because only large pharma have the financial resources to take a drug from discovery to market and for this reason many promising and potentially valuable drugs are never developed at all. The cost benefit of this cannot be calculated but would be anticipated to be very considerable.

There has, in recent years, been some movement on the drug licensing front and both the Food and Drug Administration (FDA) in the United States, the European Medicines Agency, and the British Medicines and Healthcare products Regulatory Agency (MHRA) have all advanced schemes for accelerating drug development. However, they are very cautious reforms and have been very slow to be implemented and their overall effects so far have been negligible. A more radical solution is certainly needed and this is no longer really controversial as can be seen in a survey of the topic in a special number of Reviews on Recent Clinical Trials [3].

The third cause is that while health provision is a service, the development of medicines is a business. Service and business tend to have difficulty in achieving a satisfactory working relationship as was pointed out with regard to the NHS by Douglas Black [4]. Drug discovery is frequently initiated in Academia, where the basic science is, in large part, carried out and the medicine is then developed further frequently by small companies supported by venture capital and, at a later stage, by large pharmaceutical companies who alone have the financial strength to provide the $1 billion (minimum) that is often quoted as the price of taking a drug to market. The attitudes of the scientists and the company executives to the process tend to be rather different. Underlying this difference is the question of priority of purpose; whether medicines are developed primarily to treat patients or to make money. It is indisputable that there can be a conflict between the two and that the need to make money largely dominates the field. This has another regrettable consequence which is that drugs that have achieved some success are sold at extremely high prices that bear little relation even to the unnecessarily high cost of development and certainly not the cost of manufacture but are based "on what the market will bear". Some drugs are being supplied at quite extraordinary costs as outlined by Schwartz [5] where the author quotes the nine

most expensive drugs in 2015. The most expensive drug in the world (Glybera, a gene therapy treatment for lipoprotein lipase deficiency) cost $1.3 million/year. The most expensive drug in the United States (Soliris, an antibody to C5 used to treat paroxysmal nocturnal haemoglobinuria and atypical uraemic syndrome) cost $440 thousand per year. Schwarz also gives the estimate of $1.3 trillion (1.3% of global GDP) as the total cost of prescription medicines worldwide in 2018. Unfortunately there are no signs of this situation getting any better.

A recent twist to this situation has been to take over the manufacturing facilities for a medicine that had become generic and been sold very cheaply and then put it back on the market at a hugely inflated price. The anti-epileptic Phenytoin, the anti-parasitic drug Daraprim and the Epipen injector of adrenaline for anaphylaxis are examples where such strategies have been used and have given rise to protests. This is perhaps the clearest example of where the conflict between patient benefit and financial gain is at its crudest.

There are further but lesser problems with drug supply. This is largely done through pharmacies which are separate from the doctors who prescribe them which gives rise to incremental costs, as does the fact that once a medicine has been supplied to a patient it can never is taken back if it not going to be used. Although there are clearly some safety concerns here, now that most medicines are packed as individual tablets or pills, this seems quite unnecessary and also needs reform.

There may be no quick resolution to all these problems but it is likely to be helpful if the consequences of the present regimen of medicines development and supply were more widely acknowledged and more pressure for radical reform results.

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