Innovation: New Is Not Necessarily Better

Graham Dukes

On July 29th 2002, the Honourable Mr Justice Mackay delivered in England's High Court of Justice a remarkable judgement that deserves a special place in the history of pharmaceutical law (Queen's Bench Division High Court London, 2002). Over a matter of weeks, the Court had heard and seen some of the world's leading medical statisticians - divided over two vigorously opposed groups - argue the merits of a case in which a series of women or their families had sought substantial damages from three drug companies. All three firms had marketed so-called "third-generation" oral contraceptives and the women were among those who, it was claimed, had in consequence suffered serious or fatal thromboses.

The history of thrombosis and embolism induced by the "pill" goes back more than forty years. From the early 'sixties onwards, a first generation of oral contraceptives had been on sale, typically containing 5mg of a progestogen and 150 mcg of oestrogen, and thrombotic complications resulting from their use were described from 1961 onwards. Commendably, various manufacturers set about examining the possibility of using lower doses, and in due course a "second generation" of products came into use in which the doses of both components were reduced – at first to half and later to a mere fifth of those originally employed, with a corresponding decline in thrombotic events. And so things might have remained, had not the company managements in due course been alerted to the fact that the patents on their progestogens were approaching the date of expiry, a date following which low-cost generic copies would no doubt arrive on the scene, constituting a threat to what had rapidly become a very profitable market. In due course, therefore, a "third generation" of contraceptives was developed, based on entirely new progestogenic compounds. It was however not long before evidence began

Overtoom 60 (2)
1054 HK Amsterdam
The Netherlands
+31 (0) 20 412 4523
info@haiweb.org
www.haiweb.org

to accumulate that with these new products the incidence of thrombosis had again risen; the British regulatory authority spoke indeed by 1995 of evidence pointing to a doubling of the risk as compared with the .contraceptives of the second generation (Committee on Safety of Medicines, 1995).

Before the High Court no serious evidence was advanced that the products of the third generation were in any respect better than those of the second, but there was a great deal of factual material suggesting that, where thromboembolism was concerned, they were less safe; the argument in the Court essentially came to circle around the question as to how much worse the new drugs were than those that had gone before. Remarkably, but seeking to take account of the uncertainties of medical statistics, the opposing parties had come to an agreement that if the risk of thromboembolism proved to have been at least doubled, as the British regulators had supposed, the claimants would win; if not, they would lose.

The massive judgement, without doubt the most thorough analysis of the issue ever to have been performed, concluded that, on the balance of probabilities, the move from the second to the third generation of oral contraceptives had raised the risk of thromboembolic complications by some 70%. Since the risk had therefore not clearly been doubled, the defendants escaped the claim for damages.

Although few aspects of drug efficacy or safety have been subjected in courts of law to anything approaching Mr Justice Mackay's magnificent 105-page analysis, even a cursory examination of drug innovation over the last century leads to some striking conclusions. One is that innovation has experienced various ups and downs. During an "up" period – one thinks particularly of the 'fifties and sixties of the twentieth century – important breakthroughs in medicinal treatment were achieved. It was good that the

barbiturate sedatives were supplanted from 1960 onwards by the less dangerous benzodiazepines, even though the latter were still capable of producing serious dependence. Parkinsonism became amenable to effective therapy with L-DOPA combined with an enzyme inhibitor. The mercurial diuretics disappeared with the advent of the much safer thiazides, while the treatment of hypertension either the thiazides or the beta-blockers put paid to the long era of the unpleasant rauwolfia extracts. That particular period of achievement however created great expectations; practitioners and patients looked forward to a long period of therapeutic advance in which all physical and mental ills would ultimately yield to the prescription pad; companies, for their part, foresaw an area of unprecedented financial success. Such hopes were by no means always met, but every new compound that emerged from the laboratory benefited from the optimism that had been created –and from the hyperbole with which advertisers proved capable of decking it out. Significant breakthroughs were few – in some years there seemed to be none at all - but there was at all times a vigorous inflow of new names and substances. Some indeed represented what the industry was fond of calling stages in "stepwise improvement"; many others were merely steps aside or even steps backward. The astonishing history of efforts to develop new anti-inflammatory and antirheumatic drugs illustrates the rocky road along which research may progress. It is probably still fair to regard acetylsalicylic acid ("aspirin") after 111 years as being in many respects the most successful synthetic drug of all time. True, there is in some instances a need for alternatives, and a genuine welcome awaited ibuprofen and naproxen: if one needed something a little more potent one could now turn to indomethacin, though with a greater chance of adverse effects. Other candidates for the role of "super-aspirin" fell by the wayside after brief and disastrous careers (Dukes, 1990); zomepirac (Zomax^{R})produced anaphylaxis on a massive scale; benoxaprofen (Opren^{R}), which was triumphantly trumpeted as bringing with it "a wind of change in the treatment of arthritis" killed a proportion of elderly patients by

disrupting their liver function; and rofecoxib (Vioxx[R]) was similarly withdrawn in haste after its ability to induce cardiovascular disorders became all too clear (Edwards, 2003). Other drugs in this class appear to have survived primarily by vigorously vilifying aspirin, inducing a widespread and somewhat exaggerated dread of its effects on the stomach. And did society truly benefit in any way from the ventures –some transient and others persistent - that went by the names of indoprofen, ibufenac, alcofenac, mefenamic acid, acemetacin, oxymetacin, fenclofenac, or glafenine?

In some fields, newcomers inspired on an existing example have turned out to be no better and no worse than what went before. No-one appears to be sure how many close congeners of chlordiazepoxide (the first benzodiazepine) have been synthesized since it was accidentally discovered in 1955, but the total may well run into the hundreds; the majority have been found to be closely similar to the original compound (except for some differences in their duration of action). A little further adjustment to the basic structure can however provide some unpleasant surprises; that was the case with the triazolobenzodiazepine Halcion[R], that in the doses originally identified as most effective moved some users to commit suicide or homicide (Abraham & Sheppard, 1999).

The antibiotics perhaps represent a case apart. The widespread (and often excessive) use of existing antibiotics is an ongoing invitation to the development of resistance, and where resistant strains emerge it is vital that alternative, and often newer, antibiotics be available to which the microorganisms in question are still susceptible. It seems ever more likely however that there will ultimately be serious limits to this solution; multi-resistant organisms may well prove astute at defying whatever new antibiotic is mobilized in the hope of challenging them. In the long run society must learn to use these compounds more rationally if the bacterial world is not to win the ultimate battle.

To cite this article: Graham., D. (2010). Innovation: New Is Not Necessarily Better. The Politics of Medicines (e-Encyclopaedia). Available at: https://haiweb.org/encyclopaedia/innovation-of-medication/

One sound reason to be reticent regarding the introduction of new drugs to the market where they do not carry any serious promise of new therapeutic benefit is simply the fact that no new medicine is at the time of its introduction can ever be fully documented. Even the extensive files of data demanded for regulatory purposes provide no more than the evidence derived from controlled studies, generally involving at most no more than a few hundred patients and some healthy volunteers. Once such a product enters the market many thousands or tens of thousands of individuals are likely to be exposed to it; at that time relatively uncommon side effects and interactions will come to the fore, as will information on the drug's effects in particular user groups, such as the elderly, the young and persons concurrently using other medicines. A fair proportion of new drugs are likely to be withdrawn within a few years of their introduction because of unanticipated problems. That is no reason to be fearful of new medicines as such; but it is sufficient reason to avoid taking unnecessary risks by accepting drugs for which there is no real need.

One of the few reasonable arguments that might be raised for tolerating the constant inflow of non-innovative new drugs to the market is that they serve to maintain employment and trade (including in some instances research activity) between the very occasional and unforeseeable moments when true breakthroughs emerge. No pharmaceutical company can be entirely happy to launch an uninteresting new compound; however, by developing a series of "potboilers" (or acquiring them under licence) it can at least keep its management and shareholders reasonably happy for a while in the hope of better things to come. Whether that purely commercial benefit in any sense justifies the phenomenon as a whole seems very doubtful; potboilers decked out with persuasive phrases confuse and complicate the prescribing scene. On occasion they also unnecessarily raise costs; when one American firm was faced with the impending expiry of its patent on a highly profitable antihistamine and had no worthy

To cite this article: Graham., D. (2010). Innovation: New Is Not Necessarily Better. The Politics of Medicines (e-Encyclopaedia). Available at: https://haiweb.org/encyclopaedia/innovation-of-medication/

successor to it, it developed, patented and vigorously marketed its principal metabolite as a means of retaining both a comfortable price and insurance coverage (See, 2003).

What surely cannot and should not be tolerated is the entry into the market of products that are significantly *less* acceptable in public health terms than those that have gone before and that are only likely to win favour through aggressive marketing. Some regulatory agencies indeed tend at the present day to regard the standards of efficacy and safety already attained by recognized drugs as comprising a gold standard by which newcomers will be judged; that is precisely the standard that should have led to the withdrawal of the third generation oral contraceptives once their disproportionate risks were established, notably by Mr Justice Mackay's judgement. Had it not been for the remarkable and discreditable agreement between the parties in that case regarding the degree of added risk that could be considered acceptable, this course might well have been followed and women would thereafter not have suffered and died unnecessarily.

Is society capable of introducing drug policies that will encourage and reward useful innovation, and discourage anything less? If so, can this be achieved without arresting the process of advancing therapy in one small step at a time? Norway's former "need paragraph" clearly did raise an effective legal barrier to their entry, but it succumbed to Big Pharma's consistent brainwashing of European policy makers (Abbott & Dukes, 2009) – a classic case of commercial lobbying defeating good sense. To some extent, the very existence of strict drug regulation, calling for proof of efficacy and safety, does have a beneficial effect in this matter; where a new compound appears on the basis of animal studies to bear little or no promise of improved efficacy or greater safety, pharmaceutical companies often appear to experience difficulty in finding critical and credible investigators who are willing to study it in the clinic. Health funding agencies, for their part, are setting firm pricing criteria for new products; those which appear to

be devoid of therapeutic novelty are likely to be granted a selling price hardly greater than that set for a low-cost generic. The regulation of advertising and marketing is being tightened so that it will become increasingly difficult to suggest, in the absence of sound evidence, that a medicine possesses particular advantages over its fellows. Finally, hospitals and health services are to an ever greater extent issuing limited lists of the medicines that may prescribed under their auspices, showing little willingness or none at all to permit the prescribing of drugs which bear no particular promise; in that respect, the Norwegian "need paragraph" is now enjoying a clear revival, be it at another level.

It is not impossible that the era of mediocre "me-too" drugs will at some time in the foreseeable future become less pronounced. One reason could lie in the growing move away from chemical synthesis towards a period during which biotechnological innovation will dominate the scene. In the chemical laboratory it has been relatively simple to tinker with existing molecules, adding an ethyl group here and a double bond there to create variant that can earn a patent of its own even though it promises nothing in the way of therapeutic novelty. In biotechnology that simple approach to chemical embroidery hardly exists; development costs for each new product are likely to be such as to discourage ventures bearing only dubious promise.

Whether one is dealing with medicines or with motor cars, the delusion that newer is necessarily better dies hard; it is a delusion that is akin to the belief in progress and one that is cheerfully fostered by commercial promotion. Where motor cars are concerned a little misunderstanding may not matter very greatly, but where one is dealing with medicines there is a real risk that one may too readily be tempted to abandon a well-trusted remedy for one that is perhaps built on flimsy promises, and the ultimate problems with which are still concealed in the mists of the future.

To cite this article: Graham., D. (2010). Innovation: New Is Not Necessarily Better. The Politics of Medicines (e-Encyclopaedia). Available at: https://haiweb.org/encyclopaedia/innovation-of-medication/

Abbott, F.M., Dukes, G. (2009). Considerations of Medical Need. In: *Global Pharmaceutical Policy.* Cheltenham UK and Northampton MA: Edward Elgar Publishing, pp.180-109.

Abraham, J., Sheppard, J. (1999). *The Therapeutic Nightmare. The Battle over the World's Most Controversial Sleeping Pill.* Earthscan, London.

Committee on Safety of Medicines. (1995). Combined Oral Contraceptives and Thromboembolism. *Circular letter to physicians and pharmacists*, October 18th.

Dukes, G. (1990). The Seven Pillars of Foolishness, In: Dukes, G. (Ed.): *Side Effects of Drugs Essays*. Amsterdam, New York and Oxford: Elsevier, pp 99-113.

Edwards, I.R. ed. (2003). Regulation of Vioxx: Success or Failure? *Uppsala Reports*, April, 11-13.

Queen's Bench Division High Court London. (2002). XYZ and others (Claimants) versus (1) Schering Health Care Limited, (2) Organon Laboratories Limited and (3) John Wyeth and Brother Limnited. Judgement by the Hon. Mr Justice Mackay. London, 29 July 2002. Case No. 0002638. Neutral Citation No; (2002) EXHC 1420 (QB).

See, S. (2003). Desloratadine for Allergic Rhinitis. *Am Fam Physician*, 68(10), 2015-2016.

To cite this article: Graham., D. (2010). Innovation: New Is Not Necessarily Better. The Politics of Medicines (e-Encyclopaedia). Available at: https://haiweb.org/encyclopaedia/innovation-of-medication/