

Vioxx withdrawn because of cardiovascular concerns

Merck Sharp & Dohme has announced the immediate voluntary withdrawal of Vioxx (rofecoxib). The decision is a result of concerns raised in the APPROVe (adenomatous polyp prevention in Vioxx) study, which found an increased risk of heart attack and stroke after 18 months of treatment.

All strengths and formulations of the cyclo-oxygenase-2 selective inhibitor are being withdrawn on a worldwide basis. Stocks will also be recalled from wholesalers and all clinical trials are being stopped. Limited stocks for compassionate use remain available in the short term.

"We are taking this action because we believe it best serves the interest of patients," said Raymond Gilmartin, chairman, president and chief executive officer of MSD's parent company Merck & Co Inc. "Although we believe it would have been possible to continue to market Vioxx with a licence that would incorporate these new data, given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take."

David Pruce, director of practice and quality improvement, Royal Pharmaceutical

Society, said: "Pharmacists approached by patients taking Vioxx should advise that they consult their doctor. Patients wanting to stop taking Vioxx before visiting their doctor should be offered advice on alternative painkillers. Because Vioxx is often prescribed for patients at higher risk of developing serious gastrointestinal side effects caution should be taken before recommending an over-the-counter preparation containing non-steroidal anti-inflammatory drugs."

First authorised in 1999, Vioxx is used by an estimated 400,000 patients in the UK. It is indicated for osteoarthritis, rheumatoid arthritis and short-term pain relief. The summary of product characteristics and patient information leaflets highlight the need for caution in high risk patients, after trials suggested the possibility of additional thrombotic risk.

A major study in 2000 demonstrated an increased risk of cardiovascular events with Vioxx compared with naproxen, but other studies have not shown an increased risk compared with placebo or other NSAIDs.

The APPROVe trial studied the effect of three years of treatment with Vioxx on the recurrence of neoplastic polyps of the large

Vioxx was withdrawn this week by MSD

bowel in 2,600 patients with a history of colorectal adenoma. After 18 months of treatment, patients taking Vioxx showed a higher rate of confirmed serious thrombotic events compared with placebo (6 versus 3 per 400 patient years).

Gordon Duff, chairman of the Committee on Safety of Medicines, said that the data are specific to rofecoxib and cannot be generalised to other COX-2 inhibitors.

PCTs too slow to commission new pharmacy services

Provision of new primary care services to patients is likely to be hindered by the fact that many primary care trusts have been slow to grasp their new strategic responsibilities, according to Howard Stoaite MP, chairman of the All Party Parliamentary Group on Primary Care and Public Health.

He said: "Primary care organisations have to be prepared to put their hands in their pockets and commission these new primary care services from pharmacists. If they are as slow to commission additional services from community pharmacies as they have been to commission practice-based enhanced services, then community pharmacy will struggle to achieve its potential."

Dr Stoaite explained that although part of the problem is financial caution, PCTs are small, highly localised organisations that often lack the commissioning expertise or experience to ensure delivery of new services. "PCTs will no doubt be able to develop this expertise in time as they mature as organisations," he said.

"But in the short term they may be forced to buy in help from outside if they are to fulfil their responsibilities. It is a problem which the Department of Health clearly needs to take seriously."

Dr Stoaite was speaking at the UniChem convention in South Africa this week.

Meetings p538

Put patients in driving seat

Patient choice in health care means creating services with patients in the driving seat. This was the consensus of a meeting organised on behalf of leading organisations representing pharmacy held at the Conservative Party conference this week.

Robert Meadowcroft, from the Parkinson's Disease Society, spoke about the value of expert patients and self-management and suggested that "top-down" services should be removed.

Stephen Dorrell, former health minister, said that the institutionalised boxes of social care and health care need to be broken down, and the political implications of what this would mean to the NHS in the future need to be taken seriously. He also pointed out that there was a school of thought that the more successful the health service was, and the more efficient it became, the less money should be spent on it. This was irrational, he stated. Spending money on health was a sign of an economically successful country.

GPs get new powers to commission services direct

GP practices will be able to commission services under new powers to be implemented in April 2005.

Introducing this practice-led commissioning was an aim of the NHS Improvement Plan published in June. The new powers mean that GPs can opt to receive a budget from their primary care trust and use it to fund services they choose for their local population. It will be up to individual practices to decide whether or not they wish to participate in the initiative.

A Department of Health spokeswoman told *The Journal* that pharmacists are one of the service providers from whom GPs could commission services.

Practice-led commissioning has been piloted in Bradford. Ian Rutter, a GP in Bradford, commented: "Our experience of offering practice-led commissioning has been immensely positive. It has achieved greater involvement of clinicians and practices with their patients in decisions about care."

GPs' commissioning budgets will be based on the practice's historical spend for the previous year. Practices will be expected to balance their budget over a three-year cycle and yearly overspends will be met by the PCT. PCTs will remain legally responsible for the contracting process. Any savings made by GPs commissioning services more efficiently will have to be reinvested in patient care.

The Society

Views sought on devolution

The Society is seeking members' views on how it should evolve to embrace devolution in Scotland and Wales (p541 and pp543-544).

Offer on new Martindale

A 15 per cent discount is available on early orders for the new Martindale (p542).

Evidence of harm from antioxidant supplements

Antioxidant supplements are not effective in protecting against gastrointestinal cancers, a review of trial data has revealed. What is more, the analysis showed that some combinations of supplements may slightly increase cancer risk. Only selenium was shown to be associated with risk reduction (*Lancet* 2004;364:1219).

Goran Bjelakovic and colleagues, from the Cochrane hepato-biliary group at Copenhagen University Hospital, examined data from 14 randomised controlled trials involving over 170,000 people — there were 10 different interventions and 2,100 cancer endpoints covering five sites (oesophagus, stomach, large bowel, pancreas and liver). In general, the researchers observed no evidence of benefit or harm when all five cancer sites were considered. The exceptions were vitamin C (for which there were limited data) and selenium, which seemed to exert a protective effect for gastrointestinal cancer.

In terms of harm, two combinations of supplements were found to be associated

with increased mortality: beta-carotene and vitamin A (relative risk 1.29, 95 per cent confidence interval 1.14–1.45) and the combination of beta-carotene and vitamin E (1.10, 1.01–1.20).

Writing in an accompanying editorial (*ibid*, p1193), David Foreman, University of Leeds, and Douglas Altman, Cancer Research UK, say: “Somewhat chillingly, Bjelakovic and colleagues also estimate that, despite the small size of the relative risk, if their findings are correct, 9,000 in every million users of such supplements will die prematurely as a result. The prospect that vitamin pills may not only do no good but also kill their consumers is a scary speculation given the vast quantities that are used in certain communities.”

However, they warn that the analysis is a work in progress and that the mortality findings should be seen as preliminary. “In the event that a hazard is established from a complete review, these researchers will need to identify which specific interventions are associated with any risk.”

Some combinations of supplements may increase cancer risk

Diabetes affects 1.8 million people in UK

There are now 1.8 million people with diabetes in the UK, according to new statistics released by Diabetes UK.

The charity says that this reflects an increase of 400,000 people in eight years. Of the 1.8 million almost 250,000 people have type 1 diabetes and just over 1.5 million have type 2 diabetes.

The figures are published in a report by Diabetes UK, which also estimates that there are up to a million people with type 2 diabetes who have not yet been diagnosed.

Douglas Smallwood, chief executive of Diabetes UK, said: “The challenge now is to

ensure that all people with diabetes are diagnosed early and treated effectively.”

The report, entitled “Diabetes in the UK 2004”, also looks at the impact of the long-term effects of diabetes.

The report is available via *PJ Online* (www.pjonline.com/links/pj).

□ **MeReC Briefing** Diabetes is the subject of the latest issues of *MeReC Briefing*, which consider the management of blood glucose (issue 25) and of cardiovascular risk factors (issue 26).

The briefings are available via *PJ Online* (www.pjonline.com/links/pj)

EHC prescribing falls

Prescribing of emergency hormonal contraception is falling as more women realise that there are simpler ways of obtaining it than seeing their GPs.

The latest statistics on contraception services in England show that the number of EHC prescriptions fell by 2 per cent between 2002–03 and 2003–04. This repeats a 2 per cent fall from the previous year.

However, national survey data show that the percentage of women obtaining EHC from pharmacies has fallen from 33 per cent in 2002–03 to 27 per cent in 2003–04. Conversely, the percentage obtaining EHC from walk-in centres or minor injuries units over the same two years rose from nil to 11 per cent.

□ **EHC guidance** The Royal Pharmaceutical Society has updated its guidance to pharmacists on selling EHC as a pharmacy medicine. The new guidance reflects the recent change to the dosage used from two 750µg levonorgestrel tablets taken 12 hours apart to a single dose of 1.5mg levonorgestrel taken within 72 hours of unprotected sexual intercourse.

Follow up Muslim patients during Ramadan

During Ramadan, Muslim patients often unilaterally change the intake time and dosage of drugs without taking medical advice, a recent review has found (*BMJ* 2004;329:778).

In general, adult Muslims must not consume food, beverages or oral drugs between dawn and sunset during Ramadan, the ninth month of the Islamic lunar calendar. Under Islamic rules, patients with chronic diseases are allowed not to fast but often do so.

The authors of the review point out that drug regimens need to be carefully adjusted so that all doses can be safely taken in the shorter period between sunset and dawn.

However, two surveys, covering over 400 patients, revealed that most patients change drug regimens during Ramadan, often without taking medical advice.

The authors recommend, therefore, that

Muslim patients with chronic diseases are followed up during Ramadan, so that optimal dosage regimens that account for the changes to daily routine can be established.

If therapeutic problems do occur, slow release formulations or chronotherapeutic formulations should be used, when these are available.

The authors describe several studies demonstrating the importance of considering circadian changes in the pharmacokinetic and pharmacodynamic properties of drugs during Ramadan.

However, they suggest that further studies should be carried out to provide more guidance about the ways in which the administration of drugs should be modified.

This year Ramadan is expected to start on 15 October.

In brief

Immunoglobulin in MS

Intravenous immunoglobulin cannot be recommended for patients with secondary progressive multiple sclerosis, say researchers. Patients were randomised to IV immunoglobulin or placebo, but no differences in clinical outcome measures were observed (*Lancet* 2004;364:1149).

MHRA meets its targets, but criticism continues

All the targets set for the time it takes the Medicines and Healthcare products Regulatory Agency to make medicines licensing decisions were exceeded last year. But questions continue to be asked about the quality of some of its decisions.

The MHRA annual report for 2003–04 says: "This year, the agency maintained excellent service levels in terms both of the speed with which it processed licensing applications and the quality of the decision-making process."

But within days of the report's publication, the BBC's *Panorama* programme claimed that the MHRA could have been aware of serious side effects of paroxetine (Seroxat) before the drug was licensed.

Panorama said that clinical trial results contain evidence that Seroxat can leave a quarter of all users addicted, that it may increase the risk of suicide in young adults and that rapid increases in dosage can cause serious side effects. The programme claimed that the MHRA could have known this much earlier because it had some of the confidential clinical trial information before the drug was licensed 13 years ago.



The MHRA is based at Vauxhall, near the Royal Pharmaceutical Society

In its defence, the MHRA said that the safety of paroxetine had been under continual review since it was first licensed. The agency

had acted promptly as soon as new evidence had been made available. The report of an expert working group that has been reviewing the safety and efficacy of all SSRIs in adults is due to be published at the end of the year.

In addition, MHRA chief executive Kent Woods told *Panorama* that its claim that the regulation of drugs is a secretive business that does not put safety of patients first is inaccurate.

But the annual report admits that there is a perception that the agency is unduly uncommunicative and that this impacts on the tone in which its work is reported.

As a result, a specialist communications consultancy was asked to develop a strategy and action plan for the agency. One outcome is that the new post of communications director was advertised in August. An appointment is expected soon.

This is the first annual report since the MHRA was formed from the Medicines Control Agency and Medical Devices Agency. It says that the new agency must be greater than the sum of its two constituent parts in order to maximise its role in protecting public health.

News in brief

Minimum wage rise

Minimum pay for adults rose from to £4.85 per hour and for 18–21-year-olds from £4.10 on 1 October; 16- and 17-year olds have to be paid at least £3.

CD ROM on risk

The Welsh Centre for Postgraduate Pharmaceutical Education has launched an interactive learning programme on risk management.

Complementary medicine

A series discussing different aspects of complementary medicine.
www.pjonline.com/series

Pharmaceutical societies

A partial list of pharmaceutical societies and associations around the world, including a link to the International Pharmaceutical Federation (FIP).
www.pjonline.com/links/pharmsoc

Babyloss

October 9 to 15 is Babyloss Awareness Week.
www.pjonline.com/links/children

What's new

PJ Online is continually being updated. Details of recent changes can be found on the "What's new" page or via the various "New on this site" links.
www.pjonline.com/whatsnew

OFT says Drug Tariff may impede competition

Competition may be impeded by the Drug Tariff, the Office of Fair Trading says.

Section IX of the Drug Tariff (appliances) has been used by the OFT as one of a number of a case studies in a review of the impact of public sector procurement policies on competition. The review says that the tariff is likely to affect competition in three ways: restricting price competition, hindering the acceptance of new products and distorting distribution patterns.

Price competition could be reduced, the OFT says, because there is no competitive tendering process for the inclusion of products in the tariff. Further, once they are listed, products are prescribed according to individual clinical need rather than price.

Acceptance of new products is hindered, it says, because it is easier for similar products to get a listing after an innovative product has

been put on the tariff than it is for the original product to be accepted in the first place. The report gives as an example a coated catheter that took six years to be included, yet a second near-identical product took only six months.

The OFT adds that distribution may be distorted because the different remuneration systems for pharmacy and appliance contractors give appliance contractors a financial advantage.

The OFT is currently considering, in the light of other procurement reviews, what its next steps should be. It will discuss the reviews with other Government departments, and with the Treasury-based Office of Government Commerce in particular, before deciding what action, if any, it should take. The OFT expects to announce its decision early next year.

Flu vaccine manufacturing halted by MHRA

Fluvirin influenza vaccine will not be available this year.

The Medicines and Healthcare products Regulatory Agency has suspended manufacturer Chiron's manufacturing licence for three months because of a lack of compliance with good manufacturing practice at the company's Liverpool factory.

Chiron was expected to supply 20 per cent of the flu vaccine needed in the UK this

year and half of that needed in the US. The company expects to make up some of the UK shortfall, but not the US shortage, from other European manufacturing sites.

Fluvirin has not been yet been distributed this year, so there will be no product recall. Chiron's manufacturing licence was suspended by the MHRA the day after England's chief medical officer launched this year's influenza vaccination campaign.

European paediatric research incentives not enough, says ABPI

Proposed regulations intended to encourage the pharmaceutical industry to test medicines specifically for use in children are too little and too late, according to the Association of the British Pharmaceutical Industry.

"The incentive of a six-month extension to a medicines patent for companies undertaking clinical trial work in children is a step in the right direction, but it needs to go further to attract such work into the UK and Europe," said ABPI director of medicine Richard Tiner.

The ABPI believes that the incentives should come sooner and need to be greater to attract research from the US.

A proposed European Commission regulation, published last week, follows the form drafted six months ago and offers companies marketing rewards if they carry out the extra work, regardless of whether the outcome is positive or negative (*PJ*, 20 March, p341).

In essence, companies will have to submit child-related safety data in accordance with previously agreed plans whenever they apply for a marketing authorisation, unless the product has been granted a waiver because it is unlikely to benefit children. In return, they will get an extra six months' patent protection for the active ingredient. In the case of orphan medicines, there will be an extra two years' protection.

Manufacturers of medicines that are out of patent will also be encouraged to test medicines for paediatric use. They will be able to apply for new paediatric use marketing authorisations (PUMAs) and will get 10 years' data protection so that no other maker will be able to apply for a licence on the back of the original company's work.

The earliest the plans can become law will be late in 2006, almost five years after the commission started to consider the matter.

Call for pharmacist-only medicines category

Increasing complexity and the potential risks of some new over-the-counter medicines calls for consideration of a new category of medicines, "pharmacist-only" medicines, conference participants heard this week.

This was the opinion of Terry Maguire, vice-chairman of PharmacyHealthLink, who said that simvastatin should be considered as the first in a new class of medicines. He said that the specific involvement of a pharmacist is essential to ensure adequate patient monitoring and to avoid the development of rhabdomyolysis.

Simvastatin should have been one of the first pharmacist-only medicines, he said, "and for many pharmacists it will be, as Levonelle was."

Dr Maguire said that this would not necessarily require new regulations, but could be created by the Royal Pharmaceutical Society through its ethical framework.

David Reissner, of Charles Russell solicitors pointed out that in effect pharmacist-only medicines already exist, since the Society holds the view that certain medicines liable to abuse, such as codeine linctus, should only be supplied under the supervision of a pharmacist, regardless of their legal category. He suggested that the Society could produce guidance for pharmacist-only medicines in the same way that it does for these products.

Dr Maguire and Mr Reissner were speaking at UniChem's convention in South Africa.

Meetings, p538

Joint health teaching planned for Aberdeen

Joint learning between pharmacy students at Aberdeen's Robert Gordon University and medical students at the University of Aberdeen is to be encouraged with money from the Scottish Executive.

The two institutions have been given £115,000 to help them develop a joint learning project.

Lesley Diack, project co-ordinator and lecturer in e-learning at RGU's school of pharmacy, said: "Currently, little has been achieved at undergraduate level to instil shared learning into future health and social care professionals. Scotland needs to take this forward in the next few years to be able to

provide a well trained and cohesive health and social care profession."

The universities will develop a shared learning programme for undergraduate and professional qualifying courses in medicine at the University of Aberdeen and pharmacy at RGU. It will also extend to the other health and social care students within RGU's faculty of health and social care.

Dr Diack added: "The establishment of an ethos of co-operative working among health care professionals must ultimately benefit patients. For this to be successful it has to start at undergraduate level to become embedded in any health care system."

Drug delivery image wins national competition

"Visualising drug delivery", by David McCarthy, was the winning image in the "Concepts" category of this year's Novartis/*Daily Telegraph* Visions of Science photographic awards. Mr McCarthy, an electron microscopist at the School of Pharmacy, University of London, captured the image of the polymer microcapsule containing smaller microcapsules by chance, when an air bubble burst on its surface during preparation. An exhibition of the winning images from each category begins at the Science Museum, London, this week.

Details at www.visions-of-science.co.uk.

Industrial achievement awards made at BPC

John Padfield received the AstraZeneca Industrial Achievement Award for his outstanding contribution to pharmaceutical sciences and the pharmaceutical industry. The award was presented at the British Pharmaceutical Conference in Manchester on 29 September by Ruth Duncan, science chairman of the conference. During his lecture at the awards ceremony, Dr Padfield urged delegates to have an eye on the product and associated market needs at all times, even during the early stages of research.

Also at the BPC, Chris McGuigan from the Welsh School of Pharmacy, University of Cardiff, received the GlaxoSmithKline International Achievement Award for his significant contribution to pharmaceutical sciences, which includes work on improving the treatment of infections.

BPC, p525

News in brief

ABPI code booklet

A booklet to provide NHS executives and managers with information about the Association of the British Pharmaceutical Industry code of practice, which goes beyond minimum legal requirements and seeks to ensure that the promotion of medicines is carried out in a responsible, professional and ethical manner, has been published by the ABPI.

Gel formulations set to be potential new treatments

Advances in gel formulations look set to deliver effective treatments for a variety of diseases. Scientists in India have developed a gel that is taken orally and which might be able to target diseases currently requiring drugs delivered by injection.

The research, due to be published in the journal *Polymer International*, suggests the gel could offer a way of treating diabetes, ulcerative colitis, Crohn's disease, bowel cancer, constipation and some infections.

Sunil Bajpai and Seema Dubey, from the Polymer Research Laboratory in Jabalpur, have produced a terpolymeric gel system into which a drug can be loaded. The hydrogel has been designed so that it passes through the stomach protecting the drug from stomach acids. They show that 56 per cent of the drug is released further down the gastrointestinal tract in the colon when the gel swells in response to the alkaline pH.

"The terpolymeric hydrogel system studied by our team provides an alternative to the parenteral medication of insulin. It is now necessary to carry out *in vivo* studies of this hydrogel system so that it could be further modified to produce oral delivery pills," said Dr Bajpai.

Polymer technologies driving through new oral and transdermal therapies

The scientists put vitamin B₂ in the hydrogel and studied the gel's releasing capacity in different pH conditions.

Meanwhile, the drug discovery company Henderson Morley reported developments from another gel formulation last week. The delivery system, produced in collaboration with researchers at the Welsh School of Pharmacy is being used to deliver antiviral therapies transdermally.

The technology is known as ionic contrast viral therapy (ICVT) and has resulted in a formulation that can contain stable antiviral drugs at high concentrations. The formulation also allows the drugs to be released easily, as well as pass readily through skin.

Further formulation work reported by the company has resulted in a novel adhesive dressing, currently the subject of a patent application.

Promise of immunotherapy for patients with rheumatoid arthritis

An experimental monoclonal antibody has shown promise as a treatment for rheumatoid arthritis.

Researchers tested the antibody, which binds to the 4-1BB protein (a costimulatory receptor on the surface of T cells) in a mouse model of the disease.

Mice given a control injection had joints that were heavily infiltrated with leukocytes and had synovial hyperplasia, cartilage destruction and bone erosion. In contrast, the

joints of mice treated with anti-4-1BB appeared normal and free of disease. Control mice also showed high levels of certain inflammatory cytokines that were low or undetectable in treated animals.

"A therapeutic approach based on triggering 4-1BB holds much promise," say the researchers.

They explain that the triggering of 4-1BB produced an antigen-specific expansion of interferon-producing T cells, while selectively

inhibiting the population of T cells responsible for the development of rheumatoid arthritis.

They conclude that the unique action of anti-4-1BB "provides a remarkable opportunity to treat autoimmune diseases without global immunosuppression".

The study is published in the October issue of *Nature Medicine* (2004;10:1088) and can be accessed via *PJ Online* (www.pjonline.com/links/pj).

Strontium ranelate shows efficacy in elderly population

A reduction in vertebral and non-vertebral fractures in women aged 80 years and over has been shown in a study testing the effects of strontium ranelate, a novel anti-osteoporotic agent.

Combined data from two clinical trials show that compared with placebo the drug reduces the risk of vertebral fracture by 32 per cent ($P=0.013$) and non-vertebral fracture by 31 per cent ($P=0.011$) in this elderly population.

Tim Spector, of St Thomas' Hospital, London, and UK co-ordinator for one of the studies, commented: "No other osteoporosis treatment has been studied in such depth in a very elderly population so these data are incredibly valuable to clinical practice. Strontium ranelate represents a real advance in the treatment of osteoporosis.

"Not only does it have a novel dual action on bone loss and formation, it also has a simple dosing regimen and is well tolerated. This should improve long-term compliance and give maximum benefit to our elderly patients."

A spokeswoman for Servier Laboratories, manufacturer of strontium ranelate, told *The Journal*: "The European Medicines Evaluation Agency has granted strontium ranelate a licence for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures."

She commented that strontium ranelate is the only anti-osteoporotic drug to increase bone formation and decrease bone resorption simultaneously.

"Strontium ranelate will be launched in the near future," she added.

News in brief

Vitamin analogue fights cancer

A compound derived from vitamin E reduces the size of tumours in mice, say researchers. They treated mice with a novel non-hydrolysable ether derivative of RRR- α -tocopherol and found that the compound was capable of reducing the primary tumour mass by greater than a half (*Experimental Biology and Medicine* 2004;229:954).

Cottonseed for prostate cancer

Gossypol, a drug refined from cottonseed oil, may boost the effectiveness of prostate cancer treatment. Research shows that gossypol induces apoptosis in human prostate cancer cells.