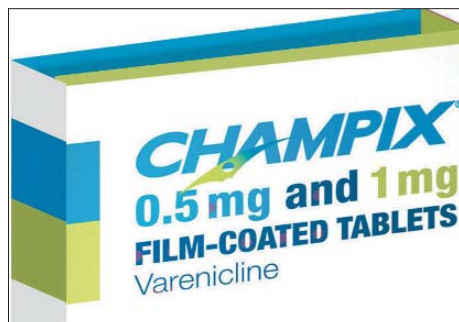


Clinical developments in 2006

More than 20 new medicines were launched in the UK in 2006. In our first CPD article of the year, **Harriet Adcock**, news editor of *The Pharmaceutical Journal*, looks back at them and considers some of the more significant clinical developments of the past year



Varenicline is a partial nicotinic receptor antagonist. Guidance on its use is expected from the National Institute for Health and Clinical Excellence in 2007

Having seen the foundations for change firmly laid in previous years, pharmacists across Britain were charged with getting on with the job in 2006.

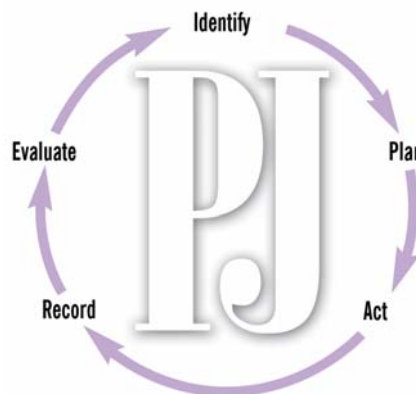
In England and Wales, medicines use reviews allowed community pharmacists to make a greater contribution to the clinical management of their patients, and the publication of template specifications for enhanced services helped ease negotiations with commissioners, leading to almost 18,000 locally agreed enhanced services being delivered under the contract before the year was out (*PJ*, 25 November 2006, p628).

A significant step in the delivery of clinical services through pharmacies came when Scotland's new community pharmacy contract began on 1 July 2006 and pharmacists were able to offer consultations through the minor ailment service (*PJ*, 1 July 2006, p3). From June, customers wanting to make use of the service were able to register with the pharmacy of their choice — the first time the public had had to register with a pharmacy to receive a national NHS service.

In Wales, there were moves to develop clinical practice when independent prescribing by pharmacists was given the go-ahead (*PJ*, 28 January 2006, p96). Meanwhile, pharmacist supplementary prescribers across Britain were getting on with the task in hand and, by the end of the year, were able to start their transition to independent prescriber status when the first two conversion courses were approved by the Royal Pharmaceutical Society (*PJ*, 16 December 2006, p724).

Pharmacists wanting to specialise in a particular clinical area were given another boost in September with the launch of a national framework for pharmacists with special interests (*PJ*, 9 September 2006, p299).

Although not directly related to the provision of clinical services, the reorganisation of primary care trusts across England caused some concern for the profession with fears



Identify knowledge gaps

1. Patients with which conditions can benefit from the POM-to-P switches that occurred in 2006?
2. Which Parkinson's disease drugs were licensed to treat restless legs syndrome in 2006?
3. In what circumstances can Exubera, an inhaled insulin product, be used within the NHS in England and Wales?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "drug therapy" (see appendix 4 of "Plan and record").

A significant step in the delivery of clinical services came when Scotland's new community pharmacy contract began

that clinical engagement could be lost if PCTs relied too heavily on practice-based commissioning for clinical involvement (*PJ*, 30 September, p384). The launch of a review of professional executive committees followed later in the year and gave pharmacy the opportunity to put its case forward on how PECs should be shaped in the future (*PJ*, 2 December 2006, p657).

In terms of new medicines, more than 20 were launched in 2006, with some genuine innovations among the batch. The first preventive therapy for cervical cancer was delivered by Sanofi Pasteur MSD and Pfizer brought an inhaled insulin product to the market.

Cardiovascular system

For medicines designed to tackle cardiovascular disease, 2006 was probably most notable for drugs that companies ceased to develop rather than for new therapies.

AstraZeneca pulled the plug on ximelagatran in February because of safety concerns (*PJ*, 25 February 2006, p222). The direct-thrombin inhibitor had been hailed as the first

oral anticoagulant since the development of warfarin more than 50 years ago but was linked to liver toxicity.

A similar fate befell torcetrapib, a drug designed to increase high-density lipoprotein levels. Pfizer decided to cut its losses in December when Phase III trial data indicated that the drug was associated with increased mortality (*PJ*, 16 December 2006, p729).

One cardiovascular drug that did make it to market in 2006 was ivabradine (Procoralan).

Ivabradine Servier's ivabradine is a potassium channel antagonist that inhibits the cardiac pacemaker I_f current. The drug, a treatment for chronic stable angina pectoris, is an alternative for patients with normal sinus rhythm who have a contraindication or intolerance to beta-blockers.

The meagre offering of new medicines to fight cardiovascular disease was augmented by licence extensions for existing therapies. Sildenafil, the erectile dysfunction therapy widely recognised as Viagra, was repackaged as Revatio when it acquired a licence for pulmonary arterial hypertension. Another drug to extend its indications was clopidogrel (Plavix), which can now be used, in combination with aspirin in patients eligible for thrombolytic therapy, for the prevention of atherothrombotic events in ST segment elevation acute myocardial infarction.

Central nervous system

In 2006 new therapeutic options emerged for patients wanting to lose weight or to quit smoking, as well as for multiple sclerosis and Parkinson's disease.

Rimonabant The first drug in a new class of anti-obesity medicines — rimonabant (Acomplia) — was launched half way through 2006 by sanofi aventis, having been beaten to market by a counterfeit. Described at its launch as a "classic example of pharmaceutical drug development", rimonabant is an oral selective cannabinoid-1 receptor antagonist. Activation of this receptor is thought to be associated with regulation of appetite, fat accumulation and with chronic tobacco use (a licence application for rimonabant as an aid to smoking cessation was made to the European Medicines Agency but was not approved). Rimonabant is licensed as an adjunct to diet and exercise for the treatment of obese patients and for overweight patients with an associated risk factor (such as type 2 diabetes or dyslipidaemia).

Varenicline Smokers who want to quit the habit but need pharmacological help have another option in the form of varenicline (Champix), launched by Pfizer towards the end of 2006. The drug is a partial nicotinic receptor antagonist, specific for the $\alpha 4\beta 2$ acetylcholine receptor. It is designed to block the "rewards" from smoking, and reduce the craving for cigarettes. Guidance on the use of varenicline within the NHS in England and



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An exciting development in oncology was the launch of Gardasil, the first preventive therapy for cervical cancer

Wales is expected to be issued by the National Institute for Health and Clinical Excellence in 2007.

Natalizumab Natalizumab (Tysabri), a humanised anti-integrin monoclonal antibody, was launched in July by Biogen Idec as a treatment for multiple sclerosis. It is thought to act by inhibiting the migration of leukocytes into the central nervous system, leading to a reduction in inflammation and demyelination. Natalizumab is licensed for the treatment of highly active relapsing remitting multiple sclerosis for patients with high disease activity despite treatment with beta-interferon and for patients with rapidly evolving severe relapsing remitting multiple sclerosis. Clinical development of natalizumab was hampered by reports of progressive multifocal leuko-encephalopathy in patients treated with the drug.

Rotigotine Patients with early-stage Parkinson's disease have another treatment option with Schwarz Pharma's rotigotine (Neupro), a dopamine agonist delivered transdermally via a patch. The drug is not an ergot-derived dopamine agonist and so does not carry the same warnings about fibrotic reactions as some other dopamine agonists. However, the Scottish Medicines Consortium failed to be sufficiently impressed when it assessed the product and rejected it for use within NHS Scotland.

Other agents acting on the central nervous system that were launched in 2006 include Novartis's darifenacin (Emselex), a urinary antispasmodic, UCB Pharma's sodium oxybate (Xyrem), a central nervous system depressant licensed for the treatment of cataplexy associated with narcolepsy, and Eisai's ziconotide (Prialt), an N-type calcium channel blocker used to treat severe, chronic pain in patients who require intrathecal analgesia.

Restless legs syndrome also surfaced in 2006 as a licensed indication for pramipexole (Mirapexin) and for ropinirole, rebranded as Adartrel.

Malignancy

One of the more exciting therapeutic developments within the field of oncology in 2006 was the launch of Gardasil, the first preventive therapy for cervical cancer and genital warts.

Gardasil A human papillomavirus quadrivalent vaccine, Gardasil, was launched by Sanofi Pasteur MSD in October. Hailed as the most important cervical cancer development since cervical screening was introduced, the vaccine is licensed for the prevention of high-grade cervical dysplasia, cervical carcinoma, high-grade vulvar dysplastic lesions and external genital warts.

Another cervical cancer vaccine is in the pipeline and is expected to be launched by GlaxoSmithKline in 2007.

A handful of new anti-cancer agents with protein kinase inhibitor activity was propelled

onto the market in 2006: sunitinib malate (Sutent; Pfizer) for gastrointestinal stromal tumours and renal cell carcinoma, sorafenib (Nexavar; Bayer) also for renal cell carcinoma, and dasatinib (Sprycel; Bristol-Myers Squibb) for chronic myeloid leukaemia. All are licensed as second-line treatments and offer hope to patients with resistance or intolerance to prior therapy.

Another new product, clofarabine (Evoltra), a purine nucleoside antimetabolite developed by Bioenvision, is available for children with acute lymphoblastic leukaemia.

Patients suffering the effects of cytotoxic agents will also benefit from products launched in 2006. Amgen's palifermin (Kepivance), a human keratinocyte growth factor, is now an option for some patients with oral mucositis. And dexrazoxane (Savene) was launched by Topo Target as a detoxifying agent for anthracycline extravasation.

The trend for product licence extensions seen in other therapeutic areas in 2006 was also apparent in oncology. Cetuximab (Erbix) was approved, in combination with radiation therapy, for the treatment of patients with locally advanced squamous cell cancer of the head and neck. And trastuzumab (Herceptin), a drug never far from the media spotlight, acquired a much anticipated indication for the treatment of patients with HER-2 positive early breast cancer.

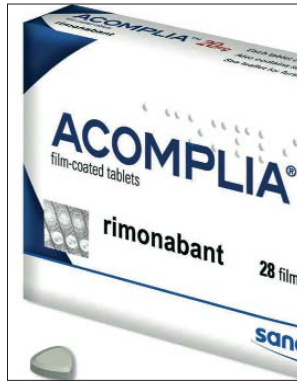
Infections

Infectious disease proved to be a productive therapeutic area for the pharmaceutical industry in 2006. Products included those targeted against hepatitis B, skin and soft tissue infections, and fungal disease.

Entecavir Patients with hepatitis B virus infection, including those who no longer benefit from treatment with lamivudine, have a new therapeutic option with entecavir (Baraclude), launched by Bristol-Myers Squibb in September. This guanosine nucleoside analogue demonstrated superior efficacy to lamivudine in Phase III trials.

Daptomycin Daptomycin (Cubicin), launched by Chiron, belongs to a new class of antibiotic and is active against Gram-positive bacteria, including methicillin and vancomycin-resistant *Staphylococcus aureus*. It is licensed for the treatment of complicated skin and soft tissue infections. A cyclic lipopeptide, daptomycin binds to the cell membranes of Gram-positive bacteria causing depolarisation, leading to rapid inhibition of protein, DNA and RNA synthesis. It is unable to penetrate the outer membrane of Gram-negative bacteria and so needs to be given with other antibacterials for mixed infections.

Tigecycline A minocycline derivative, tigecycline (Tygacil) is active against both Gram-positive and Gram-negative bacteria, including multi-drug resistant strains. Launched by Wyeth in May, this antibiotic can be used to treat complicated intra-



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abdominal infections as well as complicated skin and soft tissue infections. Tigecycline inhibits protein translation in bacteria by binding to ribosomal subunits and blocking entry of amino-acyl transfer RNA molecules into ribosomes.

Posaconazole Posaconazole (Noxafil), a triazole derivative, was launched at the beginning of last year by Schering-Plough as an antifungal agent. Its licensed indications include invasive aspergillosis, fusariosis, chromoblastomycosis and mycetoma, coccidioidomycosis and oropharyngeal candidiasis.

Eye conditions

Neovascular age-related macular degeneration was a condition that received perhaps more than its fair share of media coverage in 2006. Treatment options expanded when pegaptanib (Macugen) was launched in May.

Pegaptanib Specialists can offer patients with neovascular, or wet, age-related macular degeneration treatment with pegaptanib, an inhibitor of extracellular vascular endothelial growth factor (VEGF). VEGF activates receptors, inducing angiogenesis, and increasing vascular permeability and inflammation, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration. The drug, developed by Pfizer, is administered nine times a year by intravitreal injection into the affected eye.

Other new medicines

Other new medicines launched in 2006 include deferasirox (Exjade), an oral iron-chelating agent from Novartis. For patients with anaemias that require treatment with multiple transfusions, it offers an alternative to desferrioxamine, which is given subcutaneously over eight to 12 hours, three to seven times a week.

Also launched in 2006 were carbetocin (Pabal; Ferring), a long-acting oxytocin used to prevent uterine atony and postpartum haemorrhage after caesarean section, and erdosteine (Erdotin; Galen), a mucolytic agent used as an expectorant during acute exacerbations of chronic bronchitis in adults.

Rotarix, a vaccine against rotavirus, a cause of gastroenteritis, was launched by GlaxoSmithKline and was recognised as an innovative medicine when it received a UK Prix Galien gold medal. Two other medicines to receive this accolade in 2006 were Genzyme's alglucosidase (Myozyme), an orphan drug for the treatment of Pompe disease, and Novartis's omalizumab (Xolair), an add-on therapy for patients with severe persistent allergic asthma.

A significant step in terms of drug delivery came with the launch of the first non-injectable form of insulin. Exubera, a fast-acting, dry powder form of insulin for type 1 and type 2 diabetes is inhaled via a specially designed device. However, Pfizer's product was not well received by either NICE or the SMC. Exubera was rejected for use within NHS Scotland on economic grounds (*PJ*, 16

Rotarix, a vaccine against rotavirus, a cause of gastroenteritis, was launched by GlaxoSmithKline

September 2006, p326) and has a limited market in England and Wales, where its use is allowed only for patients with poor glycaemic control despite other therapeutic interventions and who have a diagnosed needle phobia or who suffer from severe and persistent injection site problems (*PJ*, 16 December 2006, p726).

POM-to-P switches

The steady stream of POM-to-P switches faced by pharmacists in 2004 and 2005 slowed to a trickle last year. Of note are the reclassifications from prescription-only to pharmacy-medicine status of amorolfine and sumatriptan (*PJ*, 20 May 2006, p579, and 27 May 2006, p613, respectively). Customers with fungal nail infection can now be reviewed by a pharmacist and treated with amorolfine 5 per cent nail laquer, launched as Curanail by Galderma. GlaxoSmithKline's Imigran Recovery (sumatriptan, 50mg) tablets can be supplied over the counter to migraine sufferers who are aged 18–65 years, have a history of five or more migraine attacks over a period of at least one year and have a clear diagnosis made by a doctor or pharmacist. Patients must fill in a questionnaire to establish whether OTC treatment is appropriate. The Royal Pharmaceutical Society has produced practice guidance for pharmacists on both of these switched medicines (available at www.rpsgb.org).

New guidance

NICE issued several new technology appraisals in 2006, including ones on:

- Docetaxel, paclitaxel, trastuzumab and hormonal treatments for early breast cancer
- Efalizumab and etanercept for psoriasis
- Statins

It also faced the prospect of a judicial review as it published its updated guidance on medicines used to treat Alzheimer's disease. Manufacturers were not happy with NICE's decision to restrict use of the acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine to patients with moderate Alzheimer's disease.

NICE and its collaborating centres also published several clinical guidelines during 2006. These gave advice on the management of obesity, dementia and hypertension. Other guidelines addressed urinary incontinence, anaemia in chronic kidney disease, bipolar disorder, Parkinson's disease, atrial fibrillation, tuberculosis and nutrition support.

Recommendations on the use of new drugs within NHS Scotland were issued by the SMC, often ahead of NICE guidance, and by the Scottish Intercollegiate Guidelines Network, including recommendations on the management of hepatitis C, dementia, head and neck cancer and peripheral arterial disease. Apparently conflicting guidance across the home countries led to media reports of a cross-border post code lottery.

Details of all the recommendations made by NICE, SIGN and the SMC in 2006 are

available from their websites (www.nice.org.uk, www.sign.ac.uk and www.scottishmedicines.org.uk, respectively).

New national service frameworks were not evident in 2006, although the Department of Health announced plans for an NSF for the treatment of chronic pulmonary obstructive disease, its latest priority area (*PJ*, 1 July 2006, p7).

Drug safety

Issues such as drug shortages and counterfeit medicines, which had surfaced in previous years, continued to have a bearing on clinical practice in 2006. Safety concerns were raised around selective and non-selective non-steroidal anti-inflammatory drugs, which regulators concluded carry a small risk of arterial thrombotic events when used at high doses and for long-term treatment.

Other warnings were issued for Trasylol (aprotinin), restricting its indications and highlighting the risk of renal dysfunction and for Aptivus (tipranavir), which has a risk of intracranial haemorrhage. Safety concerns also surfaced for Omnican (gadodiamide), which carries risk of nephrogenic fibrosing dermopathy or nephrogenic systemic fibrosis, Flomax (tamsulosin), linked to intraoperative floppy iris syndrome during cataract surgery and Ferriprox (deferiprone), with a risk of agranulocytosis, and risk of neurological disorders on chronic overdose.

However, no medicine was withdrawn from the UK market in 2006 because of safety issues, and there were fewer changes to marketing authorisations for safety reasons than in the five previous years. All in all, 2006 was a successful year for clinical practice. *The Journal* will continue to keep pharmacists informed of developments in 2007.

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Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Read the summary of product characteristics for Acomplia (www.medicines.org.uk). Make notes on how you would advise a patient asking how the drug compares with other anti-obesity drugs.
2. What information does the Multiple Sclerosis Society (www.mssociety.org.uk) give about Tysabri? Is this relevant to any of your patients?
3. Which were the three clinical guidelines published in 2006 most significant to your practice? Discuss with a colleague.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?