

## 2006 TRENDS A look back at pharmaceuticals in 2006: aggressive advertising cannot hide the absence of therapeutic advances

● In 2006 we analysed about a hundred new products (without counting several hundred new generics) and found that a large proportion of them were false innovations, such as me-toos and new combinations of old drugs. In brief, the R&D drought continues.

● In addition to “recycling” old products, manufacturers are increasingly seeking to create markets for their products by creating new illnesses such as metabolic syndrome: a phenomenon known as disease mongering.

● Some drugs, particularly TNF-alfa antagonists, antidepressants and cytotoxic agents, continue to be approved for a plethora of indications. More troubling, 17 drugs with negative risk-benefit balances were allowed on the market in 2006.

● Only two new drugs, nitisinone and triclabendazole, represented a therapeutic breakthrough for patients.

● Only 3 of the 7 drugs specifically designed for children and analysed in these pages in 2006 are worthy of note: metformin and the interferon alfa-2b/ribavirin combinations. There is too little evidence available about the other products to determine whether they really represent an advance for children.

● In terms of pharmacovigilance, drug regulatory agencies continue to pander to drug companies, too often satisfied with feeble half-measures, scattering safety information throughout the summary of product characteristics, and using drug companies as their mouthpiece. However, there were some

attempts to highlight specific risks of cosmetics and medical devices.

● In 2006, drug advertising and promotion continued to expand, often disguised, with massive promotional campaigns bearing no relation to the intrinsic therapeutic value of the product concerned; intense direct-to-consumer advertising of drugs designed for self-medication; so-called treatment compliance support programmes, that are in fact simply intended to get clients to keep using drugs that are losing market share; various so-called partnerships; and continued pressure from pharmaceutical sales representatives.

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In 2006 we assessed 782 drugs or indications in our French-language sister journal *la revue Prescrire*, compared to 600 in 2005. The difference was mainly due to the larger number of new indications and generic equivalents in 2006.

### Still many bogus new products

In France, many of the new drugs marketed in 2006 were in fact false innovations, reflecting the loss of R&D momentum in the pharmaceutical sector.

**New from the old.** The 50 new commercial products we examined in 2006 (excluding generics and line extensions) included:

- Eight substances that had already been marketed; the new indications were generally insignificant. These products included: azelaic acid (*la revue Prescrire* n° 268); nicotinic acid SR (*la revue Prescrire* n° 275); diclofenac (*la revue Prescrire* n° 275); single-dose oral morphine (*la revue Prescrire* n° 275); and testosterone (undecanoate) (*la revue Prescrire* n° 274). In three cases the new indication had a degree of specificity: eflornithine in hirsutism (*Prescrire International* n° 83); flurbiprofen lozenges for throat pain (*Prescrire International* n° 87) (see below); and ropinirole for restless legs syndrome (*Prescrire International* n° 85) (see below);
- Four old products, now developed for the treatment of rare diseases, giving them orphan drug status, and thus providing the manufacturers with a range of financial advantages: injectable ibuprofen (*Prescrire International* n° 85); inhaled iloprost (*Prescrire International* n° 83); levodopa + carbidopa duodenal gel (*la revue Prescrire* n° 277); and sildenafil tablets in pulmonary hypertension (*Prescrire International* n° 86);
- Six new substances very closely related to drugs already on the market (me-too), providing no tangible therapeutic advantage for patients: erlotinib (a product close to gefitinib) (*Prescrire International* n° 83); insulin glulisin (the third fast-acting insulin analogue) (*la revue Prescrire* n° 272); insulin detemir (the second long-acting insulin analogue) (*Prescrire International* n° 85); tiotropium (the third atropinic agent, following ipratropium and oxitropium) for use in chronic obstructive pulmonary disease (COPD) (*Prescrire International* n° 84); rasagiline (the second type B MAOI for Parkinson's disease, after selegiline) (*la revue Prescrire* n° 273); and pegfilgrastim (pegylated filgrastim) (*la revue Prescrire* n° 273);
- Nine combination products containing active ingredients that were already marketed individually, mainly for cardiovascular indications.

In total, truly innovative substances ►►

## Drug regulations: some advances in 2006, others eagerly awaited in 2007

Some welcome changes were made to the regulatory framework in 2006, but many others were delayed or postponed.

**The French regulatory agency is starting to take its transparency obligations seriously.** The EU Directive on human medicines places stringent demands on drug regulatory agencies as far as transparency and access to data are concerned.

A Directive becomes legally binding after the transposition deadline, and all Member States are required to ensure that their national legislation conforms to the Directive.

Signs of greater transparency appeared on the French agency's website, which last year posted the internal rules of the marketing authorisation committee, as well as minutes of meetings of the marketing authorisation committee and the national pharmacovigilance committee.

However, many data are still not available online: on 4 January 2007, only 5608 of the 17 517 existing SPCs were available online, together with 47 public assessment reports and 9 minutes of meetings. No reports were available for the second half of 2006.

As for the conflicts of interest of the experts sitting on the different agency committees, more transparency and more stringent rules are needed.

**Conditional European marketing authorisation: ensure strict application of the Regulation.** In March 2006, a Regulation dealing with "conditional" European drug approvals was adopted.

Conditional approval allows more rapid access to potentially useful drugs, but also leaves the door open to products with little therapeutic value. Transparency obligations must be respected, and conditional market approvals must not be allowed to simply become a way of speeding the clinical assessment of a new drug.

**French transposition of the Directive on human medicines: expectations and dangers.** European Directive 2004/27/EC dramatically modified the European legislative framework for human medicines. This Directive should have been transposed into French law before 30 October 2005, but, at the time of writing, the transposition law is not yet completed.

Some of the provisions of the Directive support patients' interests and are eagerly awaited; they include: Braille labelling on drug packages; prior assessment of the wording of patient leaflets by patient representatives. Other provisions on transparency, marketing authorisation, generics, etc. have already been transposed.

It should be noted that the transposition draft introduced a provision not mentioned in the Directive and created only to serve the commercial interests of drug companies: it deals with "compliance support programmes" run by drug companies (*Prescrire International* n° 83 and 87). The principal objective of these programmes is to retain clients for drugs that are losing market share: in other words these programmes have more to do with drug promotion than with healthcare and should be forbidden.

This attempt has been rejected thanks to lobbying by French members of the Medicines in Europe Forum. But the French health minister has already announced a new proposal on compliance programme for Autumn 2007.

Citizens, patients and healthcare professionals must work together to ensure that all the measures designed to ensure high-quality healthcare are fully implemented.

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### New products examined in 2006

Rating (a)	Centralised European procedure		Mutual recognition by France		French national procedure	
	Nbr	INN, indication	Nbr	INN, indication (Reference Member State)	Nbr	INN, indication
Bravo	1	nitisinone (b)	0	—	0	—
A real advance	0	—	0	—	1	triclabendazole
Offers an advantage	1	injectable ibuprofen (b)	0	—	0	—
Possibly helpful	5	eflornithine, pegfilgrastim, posaconazole (c), tipranavir, rotavirus vaccine	3	levodopa + carbidopa duodenal gel (b) (Sweden), testosterone (Finland), tetravalent vaccine booster (Germany)	1	single-dose oral morphine (refundable)
Nothing new	13	alendronic acid + colecalciferol, emtricitabin + tenefovir, erlotinib, inhaled iloprost (b), insulin detemir, insulin glulisine, posaconazole (f), rasagiline, rimonabant, rotavirus vaccine, sildenafil (b,g), varenicline, zoledronic acid (d)	8	azelaic acid (Austria), aspirin + pravastatin (United Kingdom), estradiol + drospirenone (Netherlands), ethinylestradiol + chlormadinone (Germany), omega-3 polyunsaturated fatty acids (e) (France), simvastatin + ezetimibe (Germany), tiotropium (Netherlands), trestonil (France)	6	beclomethasone, cutaneous terbinafine, diclofenac 12.5 mg, flecainide SR, hydrochlorothiazide + ramipril, hydrochlorothiazide + zofenopril
Not acceptable	5	bevacizumab, duloxetine, inhaled insulin, ivabradine, pegaptanib	3	nicotinic acid (United Kingdom), lanthane (Sweden), ropinirole (h) (Spain and Netherlands)	3	bicalutamide 150 mg (i), flurbiprofen, paracetamol + pseudoephedrine or doxylamine
Judgement reserved	2	anagrelide (b), cinacalcet	0	—	0	—
<b>Total</b>	<b>27</b>		<b>14</b>		<b>11</b>	

a- See this issue page 67 for a description of Prescrire's at-a-glance scoring system.

b- Orphan drug status.

c- In some severe fungal infections.

d- In Paget's disease.

e- In major hypertriglyceridaemia and secondary cardiovascular prevention.

f- In invasive aspergillosis.

g- In pulmonary hypertension.

h- In the restless legs syndrome. Marketing authorisation granted after arbitration for pharmacovigilance concerns.

i- In non metastatic prostate cancer. This is a specific indication for a new dose strength (150 mg) and does not apply to the existing 50 mg dose strength.

► represented barely half (23/50) the new products examined in 2006.

**Market creation or expansion.** Four of the new products examined in 2006 reflect a trend in the pharmaceutical industry: disease mongering or the invention of illnesses in order to sell medications.

For instance, rimonabant was promoted for a collection of associated disorders referred to as 'metabolic syndrome', which is irrelevant to patient care (*Prescrire International* n° 84).

Ropinirole (*Prescrire International* n° 85) and pramipexole (*Prescrire International* n° 87), two antiparkinsonian drugs, were promoted for use in restless legs syndrome, a generally harmless disorder, in which their risk-benefit balance is negative.

Paroxetine was promoted for post-traumatic stress disorder, which generally resolves without drug therapy (*la revue Prescrire* n° 277).

**Not all generic medicines are interesting.** In 2006 we examined 400 generics introduced onto the market in France, only 32 of which were new.

Some contain well evaluated substances

with proven value for some patients, such as alendronic acid, valproic acid, buprenorphine, econazole (vaginal route), gabapentin, glibenclamide, pravastatin, prednisolone and ramipril.

Others are drugs that are best avoided, such as fenofibrate and meloxicam.

In France, the market for generics continues to expand as more and more patents expire.

### Market approvals: still not enough clinical assessment prior to market release

Few of the new products examined in 2006 represented a therapeutic advance for patients: not including generics, we judged that 69 of them represented "Nothing New" in our at-a-glance rating system (see tables pages 82-84).

**A glimpse of a tree fails to reveal a forest.** In 2006, only two drugs represented breakthroughs for certain patients: – nitisinone (this issue p. 56) is the only available drug with a significant therapeutic benefit for children with type 1 tyrosinemia, a rare disease;

– triclabendazole (*Prescrire International* n° 84) is the standard treatment for fascioliasis (due to liver fluke).

**Premature market approval.** Regulatory agencies sometimes approved drugs on the basis of pre-market submissions that failed to answer many important questions. These included: – cinacalcet in parathyroid cancer (*Prescrire International* n° 83); anagrelide in essential thrombocytaemia (*Prescrire International* n° 83); letrozole for adjuvant treatment of breast cancer (*la revue Prescrire* n° 268); interferon gamma-1b in severe malignant osteopetrosis (*Prescrire International* n° 85); somatropin in low-birthweight infants (*la revue Prescrire* n° 277); and docetaxel for adjuvant treatment of breast cancer (*la revue Prescrire* n° 278).

**Too many drugs with negative risk-benefit balance.** The number of new drugs (or new indications) that were approved despite their inadequate evaluation or negative risk-benefit balance remained too high in 2006: we rated 17 products as "Not Acceptable", i.e. almost as many as in 2005. The following are a

## New indications examined in 2006

Rating (a)	Centralised European procedure		Mutual recognition		French national procedure	
	Nbr	INN, indication	Nbr	INN, indication (Reference Member State)	Nbr	INN, indication
Bravo	0	–	0	–	0	–
A real advance	0	–	0	–	0	–
Offers an advantage	4	<b>interferon alfa-2b</b> and <b>ribavirin</b> : chronic hepatitis C from age 3 years; <b>rituximab</b> : follicular lymphoma, 1 <sup>st</sup> line	1	<b>metformin</b> : type 2 diabetes from age 10 years (France)	2	<b>pravastatin</b> : after organ transplantation (b); <b>terlipressin</b> : type I hepatorenal syndrome
Possibly helpful	7	<b>adalimumab</b> : rheumatoid arthritis, 1 <sup>st</sup> line with <b>methotrexate</b> ; <b>bortezomib</b> : myeloma, 2 <sup>nd</sup> line; <b>capecitabine</b> , adjuvant in colon cancer; <b>levetiracetam</b> , partial seizures, in combination, from age 4 years; <b>temozolomide</b> , multiform glioblastoma, 1 <sup>st</sup> line; <b>7-valent pneumococcal vaccine</b> , primary vaccination at 2-5 years; <b>voriconazole</b> : candidaemia with neutropenia	1	<b>exemestane</b> : breast cancer (United Kingdom)	4	<b>IV iron</b> : anaemia related to bowel inflammation; <b>candesartan</b> : heart failure; <b>intrauterine levonorgestrel</b> device: functional menorrhagia; <b>valsartan</b> : after recent myocardial infarction
Nothing new	12	<b>adalimumab</b> : psoriatic rheumatism; <b>aprepitant</b> : prevention of vomiting due to moderately emetic chemotherapy; <b>ertapenem</b> : severe infections from age 3 months; <b>fondaparinux</b> : prevention in abdominal surgery, in medical settings, hip fracture surgery for 33 days, treatment of pulmonary embolism, patent venous thrombosis; <b>imiquimod</b> : basocellular carcinoma; <b>infliximab</b> : rheumatoid arthritis 1 <sup>st</sup> line, psoriasis; <b>oseltamivir</b> : influenza prevention in children	5	<b>escitalopram</b> : social phobia (Sweden); <b>oxaliplatin</b> : adjuvant in colon cancer (France); <b>paclitaxel</b> : adjuvant in breast cancer (Netherlands); <b>paroxetine</b> : post-traumatic stress syndrome (Netherlands); <b>perindopril</b> : stable coronary condition (France) (b)	9	<b>atorvastatin 10 mg</b> : primary cardiovascular prevention in type 2 diabetes; <b>fluoxetine</b> : bulimia (b); <b>nasal fluticasone</b> : nasal polyposis; <b>hydrochlorothiazide + losartan</b> : "severe" arterial hypertension; <b>antithymocyte immunoglobulin</b> : prevention of graft-versus-host disease after haemopoietic cell allografting; <b>nasal mometasone</b> : nasal polyposis; <b>risperidone</b> : manic episodes; <b>risperidone</b> : behavioural disorders in children with autism and mental retardation
Not acceptable	2	<b>pramipexole</b> : restless legs; <b>rivastigmine</b> : Parkinson's disease	0	—	3	<b>topiramate</b> : migraine prevention; <b>oral vinorelbine</b> : metastatic breast cancer; <b>venlafaxine</b> : social phobia
Judgement reserved	1	<b>docetaxel</b> : adjuvant in breast cancer	5	<b>interferon gamma-1b</b> : severe malignant osteopetrosis (Netherlands); <b>letrozole</b> : adjuvant after tamoxifen (France); <b>somatropin</b> : low-birth-weight infants (Denmark, Italy) (b)	0	—
<b>Total</b>	<b>26</b>		<b>12</b>		<b>18</b>	

a- See this issue page 67 for a description of Prescrire's at-a-glance scoring system.

b- Indication granted by the European marketing authorisation committee following arbitration and harmonisation.

few examples (excluding psychotropics), presented in the order of publication in our review articles:

- bevacizumab: no demonstrated survival benefit in colorectal cancer but sometimes serious adverse effects (*Prescrire International* n° 83);
- pegaptanib: its dangers outweigh its limited efficacy in macular degeneration (*Prescrire International* n° 84);
- oral vinorelbine: less effective and more adverse effects than the injectable formulation in breast cancer (*la revue Prescrire* n° 274);
- human insulin for inhalation: bronchopulmonary adverse effects not adequately studied in the long term (*Prescrire International* n° 86);
- nicotinic acid SR: very frequent adverse effects, but lack of demonstrated efficacy in cardiovascular prevention (*Prescrire International* n° 86);
- bicalutamide 150 mg in non metastatic cancer of the prostate: no gain in survival, but frequent and sometimes serious adverse effects (*la revue Prescrire* n° 276);
- sublingual desmopressin: no benefit in enuresis, and risk of confusion with the other Mimirin<sup>®</sup> formulations and dosage strengths (*la revue Prescrire* n° 276);

- paracetamol + pseudoephedrine or doxylamine combinations: risk of severe adverse effects of pseudoephedrine, just to relieve symptoms of the common cold (*la revue Prescrire* n° 277);
- lanthanum: no tangible advance for dialysis patients, but a risk of neurological and gastrointestinal disorders, and accumulation of the drug in the bone (this issue page 47).
- flurbiprofen: adverse effects of all non-steroidal antiinflammatory drugs, just to relieve sore throat (*Prescrire International* n° 87);

Another drug in this category had not yet been marketed on 31 December 2006: – ivabradin in stable angina: risk of potentially severe cardiac adverse effects and poorly assessed ocular effects, just for minor symptomatic relief (this issue page 53).

In summary, the conclusion we reached in 2005 still holds: the approval procedure is not sufficiently rigorous, either for new drugs or new indications, whether market approval is through the European centralised procedure, the mutual recognition procedure, or a national procedure (see table pages 82 and above).

**Too many psychotropics with negative risk-benefit balance.** Six (35%) of the 17 drugs with negative risk-benefit balances were psychotropics, even though psychotropics only represented 15/108 (14%) of the new products examined in 2006:

- venlafaxine in "social phobia": associated with a risk of serious cardiovascular effects, when other less risky drugs are available (*la revue Prescrire* n° 268);
- topiramate: has numerous potentially serious adverse effects that do not justify its use for the prevention of migraines (*Prescrire International* n° 84);
- duloxetine in depression and diabetic neuropathy: too risky, with uncertain efficacy (*Prescrire International* n° 85);
- ropinirole and pramipexole: restless legs syndrome (*Prescrire International* n° 85 and 87);
- rivastigmine in parkinsonian patients with dementia: causes vomiting and tremor, while only leading to (limited) cognitive benefits in 5% of patients (this issue page 66).

In light of the French health authorities' upcoming mental health programmes, this is not very reassuring (*Prescrire International* n° 82). ▶▶

### Prescribe scores for new products over the past 15 years

Rating	Number of new products or indications (a)														
	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Bravo	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1
A real advance	1	1	1	3	16 (f)	3 (h)	2	1	4 (q)	2	4	4	0	1	1
Offers an advantage	15	8	12 (d)	15	8	12	17 (l)	17	9	11	9	5	6	4	8
Possibly helpful	44 (b)	15	27	15	25 (g)	38 (i)	23 (m)	20	24 (h)	17 (s)	18	23	12	20	31
Nothing new (including generics)	69	61 (c)	65 (e)	52	85 (67)	125 (j) (81)	193 (n) (150)	165 (p) (134)	219 (r) (166)	157 (t) (121)	196 (u) (161)	133 (r) (99)	196 (v) (155)	193 (x) (155)	469 (z) (400)
Not acceptable	8	2	6	1	3	0 (k)	4 (o)	3	2	9	6 (h)	7 (h)	7 (w)	19 (y)	17 (α)
Judgement reserved	7	4	10	5	16	6	4	9	5	7	0	6 (u)	4	2	8
<b>Total</b>	<b>144</b>	<b>91</b>	<b>121</b>	<b>91</b>	<b>154</b>	<b>184</b>	<b>243</b>	<b>215</b>	<b>263</b>	<b>203</b>	<b>233</b>	<b>178</b>	<b>225</b>	<b>239</b>	<b>535</b>

a- For lack of space, this table summarises only the results for the last 15 years.

This table includes news products and indications presented to both prescribers and pharmacists by drug companies, in the community or hospital setting, and also, since 2005, range extensions (new dose strengths, new forms of existing drugs) and over-the-counter products and self-medication scored by Prescrire.

b- Including 12 insulin cartridges.

c- Including 3 insulin cartridges.

d- Including 5 somatropin-based products.

e- Including 3 insulin cartridges.

f- Including 8 products for the same indication: eradication of *Helicobacter pylori* in patients with gastroduodenal ulcer.

g- Including 7 disposable insulin pens.

h- Including 2 jointly marketed products.

i- Including 4 jointly marketed products and 2 based on somatropin.

j- Including 8 jointly marketed products and 5 based on calcitonin.

k- Four "Not Acceptable" scores attributed in 1997 were for range extensions and do not figure in this table.

l- Including 6 jointly marketed products and 1 product "authorised for temporary use".

m- Including 4 jointly marketed products, 1 product "authorised for temporary use", and 1 off-licence use.

n- Including 14 jointly marketed products, 1 off-licence use and 1 aborted marketing procedure.

o- Including 1 off-licence use.

p- Including 4 jointly marketed products.

q- Including three products re-examined after a second look.

r- Including 6 jointly marketed products.

s- Including 3 products "authorised for temporary use", 2 examined after a second look, and 1 off-licence use.

t- Including 6 jointly marketed products, 5 combinations, 5 market come-backs, 7 homeopathic products, and 5 products examined after a second look.

u- Including 4 products examined after a second look.

v- Including 2 jointly marketed products, 1 re-examined after a second look and 1 product that was never marketed.

w- Including 1 product examined after a second look.

x- Including 2 jointly marketed products and 1 product not yet marketed on 23 December 2005.

y- Including 2 products examined after a second look, 1 jointly marketed product, and 3 products not yet marketed on 31 December 2005.

z- Including 1 product examined after a second look and 4 not yet marketed on 31 December 2006.

α- Including 3 products not yet marketed on 31 December 2006.

► **Carving up of indications.** The tendency to split the indications for a given drug continues, thus creating many marketing opportunities for the manufacturers, while the benefits for patients are often slim to non-existent.

For instance, the indications for the TNF-alpha antagonists adalimumab, etanercept and infliximab were extended on several occasions to rheumatological and other disorders (psoriasis, Crohn's disease, and ulcerative colitis) (*Prescrire International* n° 82, 87).

Antidepressants are also being intensively exploited by drug companies to treat conditions other than depression: examples include venlafaxine and escitalopram for "social phobia", fluoxetine for bulimia; and paroxetine for post-traumatic stress disorder.

The same trend has existed for many years in the field of oncology, with drugs initially indicated for second-line treatment, then for first-line use, then for adjuvant therapy, etc. Witness the licence extension for bicalutamide (for the 150-mg dose strength) to non metastatic prostate cancer; bortezomib for second-line treatment of myeloma; capecitabine and oxaliplatin for adjuvant treatment of colon cancer; docetaxel for adjuvant therapy of breast cancer; letrozole for adjuvant therapy after tamoxifen; and temozolomide for newly diagnosed glioblastoma.

#### Assessment of drugs designed for children: still unsatisfactory.

In 2006 we examined the files of 7 drugs specifically designed for treatment of children. Unfortunately, not all the drugs were properly evaluated before being approved for marketing. The development of some drugs for use in the paediatric setting is welcome, such as metformin in type 2 diabetes; and the combination of ribavirin and interferon alfa-2b in chronic hepatitis C (this issue pages 50 and 63).

Other drugs were inadequately evaluated and do not provide any therapeutic advantages: levetiracetam, an antiepileptic; ertapenem, an injectable antibiotic; and nitrofurantoin (back on the market for the prevention of urinary tract infections).

Risperidone, for children with behavioural disorders associated with mental disabilities or autism, has no tangible advantages over haloperidol or lithium.

Implementation of the European regulation on drugs for paediatric use must be closely monitored.



#### Pharmacovigilance: drug regulatory agencies too lenient with drug companies

When it came to adverse effects, regulatory agencies continued to side with drug companies in 2006, and to limit market withdrawals and other measures that might affect sales or profits, even if it meant exposing patients to well documented and sometimes severe adverse effects.

#### Pathetic half-measures.

According to article 117 of European Directive 2004/27/EC on human medicines, drugs with negative risk-benefit balances can be withdrawn from the market.

Yet, after their product had been on the market for 8 months, it was the manufacturer, and not the health authorities, that asked for the market withdrawal of melagatran and ximelagatran in Europe, because of a risk of liver damage that had actually been identified before they were introduced. The US Food and Drug Administration (FDA) refused to approve these drugs in the first place.

We are still waiting for the French agency to take action on the following issues:

- the dextropropoxyphen + paracetamol combination, still prescribed in France but withdrawn from the market in Switzerland and Sweden (and soon to be withdrawn in the UK) because of serious adverse effects;
- benfluorex, an amphetamine-like drug, is still marketed in France (since 1976) despite the risks of severe arterial hypertension and heart valve damage. Benfluorex was banned in Spain in 2003. In 2006 the French national pharmacovigilance committee only recommended further research on risks associated with benfluorex;
- veralipride, a neuroleptic prescribed for ‘hot flushes’, can cause a parkinsonian syndrome and has no proven efficacy. The French agency only demanded that the SPC recommends a 3-month treatment limit. Veralipride was banned in Spain in 2005;
- buflomedil, a vasodilator with no proven therapeutic value. Serious neurological and cardiac adverse effects led the French agency to withdraw the 300-mg tablets, but not the 150-mg tablets or the injectable form, both of which are associated with the same adverse effects.

**Warnings dispersed throughout the SPC.** It is not always easy to identify changes to an SPC in response to reports of adverse effects, because they are scattered throughout the various sections (Warnings, Adverse Effects, Pharmacodynamics, etc.). In 2006, we reported on:

- ribavirin and dental adverse effects;
- infliximab and the risk of cancer in smokers;
- orlistat and bone fractures in adolescents;
- nitrofurantoin and pulmonary, hepatic, neurological and cutaneous risks;
- sirolimus and angioedema during concomitant use with an angiotensin-converting-enzyme inhibitor (ACE inhibitor);
- telithromycin and QT prolongation and severe hepatitis;
- sustained-release risperidone for injection and resurgent delirium and treatment failure.

**Pregnancy and contraception: limited information in view of the risks.** In 2006, newly identified risks associated with drug use during pregnancy included:

- a change in the Pregnancy section of the SPC for products containing paroxetine, due to a risk of cardiac malformations when paroxetine is used during pregnancy. It should be noted that all selective serotonin reuptake inhibitor antidepressants increase the risk of congenital malformations;
- an EMEA warning on the risk of ►►

## Advertising: rapidly expanding, and increasingly aimed directly at patients

In 2006, drug companies and their communications advisors further diversified their advertising methods.

**Advertising disproportionate to therapeutic value.** 2006 saw noisy prelaunch promotional campaigns for an anti-obesity drug, rimonabant, and a drug for smoking cessation, varenicline.

These drugs, both of which have little therapeutic value, were heavily promoted by the companies concerned, well before they appeared on the market: a “scientific brochure” on rimonabant was posted online, in the Investments section of the Sanofi Aventis website, and varenicline was extensively promoted on the Pfizer website and in the media.

**Direct-to-consumer advertising: drug companies’ recurring dream.** In Europe, direct-to-consumer advertising (DTCA) of prescription drugs is still forbidden.

In France, drugs available without a prescription, which have an ‘advertising visa’, can be promoted directly to the public. In 2006, this was the case for many generics and for three new drugs: nasal beclomethasone in allergy; the paracetamol + pseudoephedrine or doxylamine combination for the common cold; and terbinafine cream for intertrigo between the toes.

Some substances contained in products promoted directly to the public can have serious adverse effects. And these risks are bound to increase as the market for self-medication products expands.

**Promotion masquerading as company-sponsored compliance support programmes.** In France, a draft legislation (see inset p. 81) aiming to allow drug companies, through physicians, to create compliance support programmes based on telephone reminders, personalised patient education, home visits by nurses, was rejected in early 2007, but is due to come back in Autumn 2007.

Drug companies are not in a good position to provide this type of service, because of their obvious conflicts of interest. In addition, a quick glance at the programmes already announced is sufficient to see that they are first and foremost a way of retaining clients for drugs that provide no therapeutic advantage.



**Partnerships mainly benefiting drug companies.** Drug companies and their communications advisors are brimming with ideas to promote their products: last year saw company ads in a non-profit medical institution (*la revue Prescrire* n° 271); healthcare professionals participating in ad design, and “health information” that plays on the public’s fears (*la revue Prescrire* n° 278). Food manufacturers and even insurance companies used health issues to promote their products (*la revue Prescrire* n° 268).

**Pharmaceutical sales representatives (reps): not a useful way to improve healthcare.** After 15 years of monitoring sales reps, our assessment has not changed: there is nothing to be gained in terms of the quality of healthcare by listening to sales reps. Reps are just another promotional tool and must not be confused with reliable information sources.

For example, one company invited healthcare professionals to replace heptaminol, which was no longer reimbursed in March 2006, with dihydroergotamine, a drug that is still reimbursed (*la revue Prescrire* n° 276).

**Few prohibitions of ads for healthcare professionals, despite major infringements.** The French committee responsible for controlling advertising aimed at healthcare professionals remained below the horizon in 2006. According to the French Official Journal, only 16 ads were judged to be illegal (*la revue Prescrire* n° 268, 270, 274, 280). The reasons for these prohibitions reflect worrying trends: promotion of unapproved indications; minimisation of risks of adverse effects; and erroneous interpretation of efficacy data. If drug advertising to healthcare professionals has stooped to this level, one wonders what abuses direct-to-consumer advertising might bring!

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► oral contraceptive failure in women treated with orlistat.

**Regulatory agencies using drug companies as their mouthpiece: a confusion of roles.** Statements posted on the websites of the French and European regulatory agencies are welcome but, unfortunately, in most cases, the agencies simply distribute letters bearing a drug company logo. This promotes the company's image and reduces the agency's workload, but it does nothing to improve the credibility of either the regulatory agency or the company.

As part of a public consultation on pharmacovigilance in Europe, launched by the European Commission, we requested that drug companies be excluded from the pharmacovigilance decision-making process (*Prescrire International* n° 84).

**Medical device surveillance: attention!** Regulatory requirements for medical devices are even less stringent than for drugs, explaining why the risk of severe adverse effects is better determined once a product is already on the market. Examples in 2006 included:

- the medical device Enteryx° (a polymer-solvent mix for the treatment of gastroesophageal reflux) was withdrawn from the market following reports of serious adverse effects (pneumonia, atelectasis, mediastinitis, pericarditis, renal failure) and one death (*la revue Prescrire* n° 268);
- a survey of slings used to treat urinary incontinence showed that complications occurred in an estimated 9% of patients;
- warnings were issued concerning repeated foetal ultrasound scans simply for the parents' pleasure rather than for diagnosis or detection of malformations;
- the death of a newborn highlighted

the risk of hyperthermia associated with some phototherapy devices.

### **In short, too much promotion, too little therapeutic advance**

Incapable of bringing new products that provide real therapeutic advances to the market, drug companies are none the less showing a real talent for innovation when it comes to promoting their existing products, through partnerships, so-called disease awareness campaigns (disease mongering), and compliance programmes that in fact simply aim to increase drug use. Meanwhile, despite an increased openness, regulatory agencies, still largely financed by drug companies, are turning a blind eye to these abuses. And the charter on drug company communication via the internet, published on the French regulatory agency's website, is unlikely to prevent such abuses.

In 2006 governments again failed to persuade observers that their main con-

cerns were patients' best interests and public health. On the contrary, what seems to be uppermost in the minds of regulators and decision-makers is to avoid too much interference with private financial interests within the pharmaceutical sector! We are eagerly awaiting the adoption of some regulatory measures in 2007 that will benefit patients first and foremost.

In practice, health professionals must inform their patients of the traps of disguised drug promotion and "health information" distributed by drug companies. They must also make patients aware of the importance of conflicts of interest in medical information, and the bias resulting from governments that pay more attention to the financial health of the pharmaceuticals sector than to public health.

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### Attachment

A *Prescrire* Position is attached to this issue :

"Broad coalition opposes pharmaceutical industry control over health information"