things are unlikely to change much in 2005, judging from the "weekend training sessions" on ezetimib (Ezetrol°, MSD Chibret) that were offered to prescribers in early 2004.

Exaggerated benefits and lack of attention to risks. In 2004, 35% of the indications for drugs that sales reps promoted to Network members were not mentioned in the corresponding SPC. In nearly all of these cases, reps systematically extended the indications, and they simply invented off-licence uses in 9% of cases. The doses they recommended were also higher than those mentioned in the SPC in 15% of cases.

The reps seen by Network members were careful to minimize the risks associated with the products they promoted. For example, they only volunteered complete information concerning contraindications in 8% of cases and partial information in 15% of cases. The respective rates were 9% and 13% for precautions for use, 6% and 15% for interactions, and 13% and 17% for adverse effects. Thus, despite the numerous pharmacovigilance scandals that occurred in 2004, the quality of the information that medical reps provide on the risks associated with the products they promote has hardly improved: the same figures have been found in the last 14 years (7,8).

Cut-throat competition. If the terms of the Charter were respected, relationships between competing firms would be cordial and polite (6).

However, in 2004, as in previous years, Network members found that medical reps were increasingly aggressive towards their competitors. The most intense in-fighting in 2004 focused on the sartans, and on cetirizine, a product whose patent recently expired. A similar feeding frenzy occurred when rofecoxib, a Cox-2 inhibitor, was withdrawn from the market.

1- Cristofari JJ "Les habits neufs du marketing pharma" *Pharmaceutiques* 2004; (117): 56-59.
2- Le Masson S "La visite médicale s'externalise de plus en plus" *Pharmaceutiques* 2004; (120): 63.
3- Jarrige C "La nouvelle panoplie de la promotion" *Pharmaceutiques* 2005; (123): 41-45.
4- Prescrire Rédaction "Visite médicale: surtout un engin de guerre entre firmes" *Rev Prescrire* 2004; **24** (247): 104.
5- Prescrire Rédaction "Les prétentions de la firme Pfizer" *Rev Prescrire* 2004; **24** (251): 432.
6- "Charte de la visite médicale" 22 December 2004. Website http://www.leem.org
7- Prescrire Editorial Staff "Report by Prescrire reps monitoring on sales representatives" *Prescrire Int* 1999; **8** (41): 86-89.
8- Prescrire Editorial Staff "Prescrire's sales reps monitoring network" *Prescrire Int* 2004; **13** (71): 116.

PRESCRIRE VIEWPOINT

Translated from ***Rev Prescrire*** **December 2004; 24 (256): 827**

Still too many analgesic mixtures

In the early 1980s many preparations sold over the counter in France contained up to eight active substances with various effects, such as nonsteroidal antiinflammatory drugs, caffeine, opiates, barbiturates and antihistamines.

"Anti-mixture" measures in 1982. Work by the French health authorities led to welcome but partial changes in composition, such as the withdrawal of amidopyrine (a pyrazole analgesic); prescription drug status for noramidopyrine (risk of agranulocytosis) and phenacetin (an antipyretic analgesic carrying a risk of nephropathy, haemolytic anemia and methemoglobinemia); and a total dose limit of 8 grams for boxes of paracetamol (to reduce the risk of liver damage after overdose) (1-4).

Further improvements in the 1990s. The composition of some analgesic-based preparations has since been further simplified, such as the gradual disappearance of phenacetin (5); barbiturates (6,7); butalbital (8); quinine derivatives (9); and clearance of bromide from one product (10,11,12). Note that that these changes often consisted of replacing one substance with another, considered less harmful (paracetamol replacing phenacetin, for example).

The French medicines agency era: bad analgesic mixtures still on the market. Analgesic combinations containing three or even four active substances are still on the French market, usually with authorisations decades old. It is well known that these combinations have a negative risk-benefit balance, notably because of additive adverse effects, drug interactions, and risks associated with concurrent intake of another preparation containing the same substances.

Several obsolete substances are still available, such as belladonna powder combined with codeine, caffeine and paracetamol, and opium powder combined with paracetamol and caffeine. Caffeine is ubiquitous, despite the lack of proven analgesic effects and the known risks of excitatory and anxiogenic effects (13). Examples are products containing caffeine combined with aspirin and paracetamol; aspirin and meadow queen (Filipendula maria); paracetamol and codeine; paracetamol and dextropropoxyphene; aspirin and codeine; and a "homeopathic" product containing tinctures of belladonna and other substances combined with standard doses of aspirin and caffeine.

These mixtures have numerous disadvantages, including a risk of additive adverse effects and interactions; different regulatory statuses; risks of interactions with dietary components (especially alcohol and caffeine); various trade names bearing little relevance to the nature of the components; and uninformative packaging (international non proprietary names mentioned in small print on the side of the box but not on the blisters); and incoherent patient information leaflets (**a**).

The French medicines agency seems simply to ignore these facts, doing nothing to withdraw these mixtures from the market.

European measures to be applied in France. European Directive 2004/27/EC stipulates that fixed-dose combinations containing up to three active substances must mention all three international non proprietary names on the outer and inner packaging (14). And, hopefully, the new obligation that information leaflets be tested on panels of potential users will further underline the incoherence of such mixtures.

a- Such combinations can lead to inconsistent patient information leaflets. For example, the Precautions section of the Prontalgine° leaflet specifies that "this drug can cause insomnia and must not be taken at the end of day", while the section on Driving and Machine Use draws attention to the risk of drowsiness.

1- Ministère de la Santé - Direction de la Pharmacie et du Médicament "Synthèse des décisions prises sur les antalgiques" January 1982: 3 pages.
2- Prescrire Rédaction "Modifications de formules" *Rev Prescrire* 1982; **2** (12): 7-8.
3- Prescrire Rédaction "Quelques notes sur… Les changements de formules antalgiques" *Rev Prescrire* 1982; **2** (13): 3.
4- Prescrire Rédaction "Modifications de formules" *Rev Prescrire* 1982; **2** (14): 4.
5- Prescrire Rédaction "Changement de composition: Sédaspir°" *Rev Prescrire* 1989; **9** (85): 200.
6- Prescrire Rédaction "Changement de composition: Céquinyl°" *Rev Prescrire* 1993; **13** (132): 454.
7- Prescrire Rédaction "Changement de composition: Prontalgine°" *Rev Prescrire* 1993; **13** (130): 327.
8- Prescrire Rédaction "Changement de composition: Optalidon°" *Rev Prescrire* 1991; **11** (103): 16.
9- Prescrire Rédaction "Changement de composition: Céquinyl°" *Rev Prescrire* 1999; **19** (197): 515.
10- Prescrire Rédaction "Changement de composition: Prontalgine°" *Rev Prescrire* 1998; **18** (188): 672.
11- Prescrire Rédaction "Changement de composition: Céphyl°" *Rev Prescrire* 1999; **19** (193): 198.
12- Prescrire Rédaction "Changement de composition: Polypirine°" *Rev Prescrire* 1999; **19** (198): 595.
13- "Caffeine". In: "Martindale - The complete drug reference" 34th ed, The Pharmaceutical Press, London 2005: 782-784.
14- Prescrire Editorial Staff "Medicines In Europe: the most important changes in the new legislation" available free at http://www.prescrire.org/aLaUne/dossierEuropeSynthese2En.php