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Lingering objections to EC's pharmaceutical vision

Objections to the European Commission (EC)'s proposals to allow pharmaceutical companies to provide direct-to-consumer information on prescription-only drugs are continuing. This is despite the EC's move to exclude the mass media – TV, radio and general print publications – from those outlets allowed to carry the information.

The *BMJ* carried a letter from the student global health network, Medsin (*doi:10.1136/bmj.b290*) stating that, 'The description of information in the European proposals is inadequate and may come with some of the negative side effects of direct to consumer advertising.'

'We call on the EC to abandon its proposals and explore options for providing a more impartial and unprejudiced system of high quality peer reviewed information.'

Another letter from campaign group Picker Institute Europe (*doi:10.1136/bmj.b291*) noted that the proposal 'has already been significantly watered down.'

'The proposal can be defeated if patient and professional groups make their views known to members of the European parliament and to member governments, both of whom will need to approve the measures before they become law.'

The EC's stated aim is 'to enable citizens to have access to high-quality information on prescription-only medicines'. It is part of a pharmaceutical package, put forward by the Directorate-General for enterprise and industry, 'with the overarching objective of ensuring that European citizens can increasingly benefit from a competitive industry that generates safe, innovative and accessible medicines.'

The problem, according to the EC, is that EC citizens have unequal access to information. Although advertising of prescription-only medicines to the general public is forbidden, 'a lack of detail on information provision has led to a situation in which Member States interpret EU legislation in very different ways and have developed divergent practices on the provision of information on medicinal products.'

To address the situation, the EC adopted a Communication and three legislative proposals in December, 2008. They are due to be debated in the European Parliament and in the Council.

EC Vice-President Günter Verheugen, responsible for enterprise and industry, said after the adoption, 'Everything we are suggesting today builds on the needs and interests of patients. European citizens should benefit from safe, innovative and accessible medicines. They should be best informed about available medicines and treatments – since their health is at stake.'

The EC's impact assessment defined as 'push' information that which is passively received through TV and radio programmes and print, and through materials actively distributed. By contrast, 'pull' information is searched for by citizens and includes information on internet websites, or that provided by industry in response to patients' enquiries.

It concluded that the possibility of negative impacts appears to be particularly associated with 'push' information and said, 'The legal proposal should not generally allow mass media to distribute information on prescription medicines to the general public.

'Hence, the recommended approach is to restrict information provision to 'pull' information provided to patients who actively seek it (including information disseminated through internet websites), to patients who already have a prescription for the drug and certain printed information having a clear positive public health impact.'

This restriction has satisfied many potential critics. Catherine Foot, head of policy at Cancer Research UK, said that the aim of the Directive was to improve the provision of information in parts of Europe where it is poor. Earlier versions of the proposal had been worrying, though: 'Of course we had concerns about what this would mean for the quality and potential bias of information given to patients.'

'But the latest versions of the Directive aren't of great concern as far as the UK is concerned. As the Directive stands, its impact here will be slight because of the extent and quality of unbiased patient information provided by the National Health Service and also non-governmental organisations like Cancer Research UK.

'It is good to see that the current plans have clearly been influenced by the concerns of patient organisations. The Commission has listened to the other side of the argument,' she said.

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EMEA consults on orphan drugs...

The European Medicines Agency (EMEA) and the European Commission have opened a consultation on the criteria for orphan designation for drugs. A consultation document is available on the EMEA website (www.emea.europa.eu/pdfs/human/comp/1589309en.pdfs).

The discussion paper outlines, first, the level of evidence normally required to support the medical plausibility of using the product in the applied condition, and, second, the level of evidence required to support the assumption of significant benefit.

EMEA states that the paper is 'based on the experience accumulated over recent years with several hundred orphan drug designation applications'. About 70% of these applications included a discussion on significant benefit.

The deadline for comments, which should be sent by email to orphandrugs@emea.europa.eu, is July 2009.

. . . and establishes a new committee

EMEA has announced the creation of its 6th scientific committee, the Committee for Advanced Therapies (CAT), which met for the first time in January 2009.

It was formed following new legislation on the regulation of advanced therapies (EC No 1394/2007) and will play a central role in the assessment of innovative medicines based on gene therapy, somatic cell therapy and tissue engineering.

CAT will prepare a draft opinion on each advanced therapy submitted to the EMEA for evaluation, prior to the adoption of a final opinion by the Committee for Medicinal Products for Human Use (CHMP), which retains overall responsibility for scientific evaluation of human medicines at the EMEA.

The establishment of the CAT 'will help pharmaceutical companies, in particular small and medium-sized ones, to unleash their innovative potential and bring new medicines to the market.' said EMEA Executive Director Thomas Lönngren.

NICE reversal on myeloma and kidney cancer drugs

The UK's National Institute for Health and Clinical Excellence (NICE) has reopened consultation on the availability of drugs to treat myeloma and kidney cancer, which were previously rejected on cost grounds. The move follows NICE's initiative to relax cost-effectiveness criteria under certain circumstances when patients are close to death (see EJC News *EJC 2009;45:497*), and concessions on costs by manufacturers.

NICE's Appraisal Committee considered lenalidomide, in combination with dexamethasone, for the treatment of multiple myeloma in people who have received two or more prior therapies. Preliminary recommendations are for a cost-sharing deal under which the UK's National Health Service (NHS) will pay for the first 2 years of treatment; manufacturer Celgene will meet drug costs (but not associated treatment costs) for people who remain on lenalidomide for longer.

People with multiple myeloma who are currently receiving lenalidomide but who have not received 2 or more prior therapies, 'should have the option to continue therapy until they and their clinicians consider it appropriate to stop.'

The recommendations on lenalidomide were preliminary at the time of going to press; comments could be submitted until 20 February 2009, and the Appraisal Committee was expected to issue its Final Appraisal Determination (FAD) after a meeting early in March.

Meanwhile, NICE is also reappraising the use of treatments for renal cell carcinoma (RCC). It has issued a FAD recommending first-line sunitinib malate (Sutent) in advanced and/or metastatic RCC for patients who are suitable for immunotherapy with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

In a separate appraisal, bevacizumab, sorafenib, and temsirolimus were not recommended as first-line treatment options. Sorafenib and sunitinib, which are both licensed for second-line treatment, did not receive NICE's recommendation for use in this indication.

A statement from NICE noted: 'The previous draft of this guidance, although acknowledging that sunitinib is a clinically effective treatment, concluded that it was not a cost effective use of NHS resources.'

'After applying NICE's new arrangements for taking into account the added value society puts on treatments that extend life at the end of life, as well as the manufacturer's proposed pricing scheme which provides the first cycle of sunitinib free to the NHS, the NICE independent advisory Committee concluded that sunitinib does represent a cost effective use of NHS resources when used as a first-line treatment for advanced and/or metastatic RCC.'

Consultation on the drugs and indications which were not recommended was due to continue until 4th March, 2009.

Cetuximab 'lowers survival'

Adding cetuximab to standard first-line treatment for inoperable metastatic colon cancer significantly reduced progression-free survival (PFS) and led to inferior quality of life, researchers from the Netherlands found (*N Eng J Med* 2009:**360**:563–72).

Patients with previously untreated metastatic colorectal cancer were randomly assigned to chemotherapy (capecitabine, oxaliplatin and bevacizumab) or the same regimen plus cetuximab. Median PFS among 378 patients in the chemotherapy group was 10.7 months, compared to 9.4 months among the 377 who also received cetuximab. Quality of life scores were lower in the cetuximab group; patients also had more grade 3 or 4 adverse effects.

Mutation status of the *KRAS* gene predicted outcome; in the cetuximab group, patients with mutated *KRAS* had significantly decreased PFS, compared to those with the wild-type (or those with mutated *KRAS* in the chemotherapy-only group).

EUROFILE

The impact of the economic recession

As Europe enters into an economic recession, oncologists and health economists around the EU are becoming increasingly concerned about its effects on cancer treatment and care.

Reimbursement for cancer drugs and treatment in Europe varies considerably from country to country, with only a few, such as France, paying all the costs. 'We can hope that in countries with comprehensive healthcare, the momentum of the system will carry them through the recession,' says Richard Sullivan, (London School of Economics, UK). 'But in countries where there are similar co-payment systems to the US and out of pocket expenses involved – such as in central and eastern Europe – any downturn in the economy is going to have the same effect as in the US.'

Americans have been cutting back on their cancer treatment. 'Patients are asking what they can drop,' says Sullivan. On a statistical level, it's hitting aftercare. Patients are having the surgery and keeping their fingers crossed.'

The same sort of 'skipped care phenomena' that have been seen in the US are already occurring in Latvia, according to Sergejs Kuznecovs at the Cancer Patient Advocacy Bureau in Riga. 'Treatments are already being delayed, and now with a recession, it's getting worse,' he says.

Even though the state pays for diagnostic procedures and treatment, poverty still affects behaviour, in part because supportive care after treatment is not covered. 'Patients need to work, and many are working through their chemotherapy courses,' explains Kuznecovs. 'People are also very afraid of being disabled after surgery or chemotherapy, so they are not going for treatment.'

In Estonia, diagnostic procedures and treatment of all solid tumours and haematological cancers are covered by the national 'Sick Fund'. All intravenous drugs are reimbursed and, where patients have to pay, the percentage is quite low. However, new higher priced drugs with high survival benefits are no longer being considered for reimbursement.

'Plans to consider higher priced drugs have been frozen because of the economic recession,' says Vahur Valvere, oncologist and chairman of the Estonian Cancer Society. 'Fortunately, the overall situation is stable at the moment. The Sick Fund in Estonia is not badly financed compared to other Baltic states like Lithuania or some central and eastern European countries. If the crisis continues, we don't know what will happen – we don't know about next year.'

Oncologists in France are keeping a critical eye on reimbursements for new drugs. 'In France, if a drug brings additional survival it is usually reimbursed regardless of its cost,' explains Jean-Charles Soria, head of the phase I programme at the Gustave Roussy Cancer Institute, and chair of the French national programme on lung cancer. 'However, we are entering a new paradigm of reimbursement. At the end of 2008, the French authorities didn't accept Tarceva [for reimbursement], a drug for pancreatic cancer with clear survival benefits. This will become an area of political debate. They will need to clarify their criteria.'

'IT'S HITTING AFTERCARE. PATIENTS HAVE THE SURGERY, THEN KEEP THEIR FINGERS CROSSED'

Soria does not see an immediate impact of the economic downturn on reimbursements, therapies, and palliative care. 'However, it could impact on decisions in the mid-term,' he continues.

The issues are different in Sweden, which also boasts a comprehensive healthcare system. 'Skipped care will never be the case in Sweden and there will be no reduction in standard care,' says Håkan Mellstedt, former president of the European Medical Oncology Society and the administrative director of the cancer centre at the Karolinska Hospital in Stockholm. Instead, the impact will be felt be through staff cuts. At the Karolinska, 900 jobs are to be axed this year, including staff up for retirement who will not be replaced.

'Letting go of staff is a sign of the economic crisis. It's the same for many other hospitals in Sweden,' Mellstedt says. 'Reduced staff numbers will delay taking in-patients. If previously hospitalised, we'd treat more patients on an out-patient basis. Aftercare will be passed on to the patient's family and there will be more burden on the patients and families themselves.' He expects it will take three to four years before staffing levels are resumed.

'PLANS TO CONSIDER HIGHER PRICED DRUGS HAVE BEEN FROZEN'

In Spain the recession is not currently having an impact on drug re-imbursement, but it is affecting prevention. This is most noticeable with colorectal cancer, the nation's most frequently occurring cancer, according to Leticia Moral, oncologist and chair of the Madrid branch of the AECC, the Spanish association against cancer.

'Only three regions offer colorectal screening – Valencia, Murcia and Catalonia. Other authorities are decreasing investment in hospitals and unwilling to spend on screening,' explains Moral. 'The economic crisis is also stalling the introduction of new treatments and techniques that are not already in the system. It's another big problem.'

The pharmaceuticals industry is keeping a careful watch on the speed at which new medicines are introduced, as an indicator of how hard the recession is biting. 'This is the area to look at and see if the numbers have come down' says Colin Mackay, spokesperson for the European Federation of Pharmaceuticals Industry Associations. 'It's probably too early to tell, but healthcare funding will be squeezed.' But the end result need not be bad news for the industry. 'With a reduction in reimbursement and co-payment, countries would go towards prevention,' he thinks, 'but every cloud has a silver lining, if it forces governments to work with industry in setting priorities.'

Saffina Rana, Brussels

World Cancer Day: Focus on excess body weight

The International Union Against Cancer (UICC) has launched a campaign to raise awareness about the link between excess body weight and cancer. A report released on World Cancer Day (4 February, 2009) kicks off the year-long initiative.

It found that 40% of people in the Americas, Australia/New Zealand and western Asia were unaware that being overweight increased their risk of cancer. Awareness was even lower in other regions.

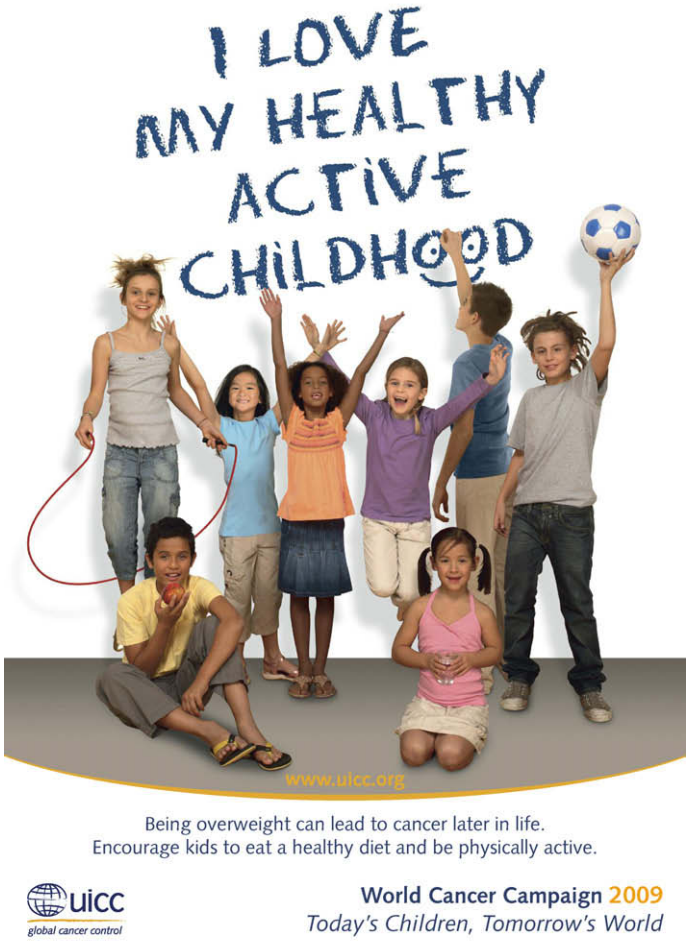
UICC's executive director Isabel Mortara said, 'Good habits start early in life, so our focus is on encouraging children to eat a healthy diet and be physically active. An estimated 22 million children under 5 are overweight today, and the problem is growing.'

Professor David Hill (Victoria, Australia), president of UICC said, 'Overweight and obesity are part of the causal chain for many cancers. This is well established in science but not adequately understood in the community. In fact, current lack of public understanding of the link between body weight and cancer probably parallels our attitudes to smoking and cancer in the late 1950s.'

The UICC's campaign aims to encourage parents, teachers, health professionals and decision-makers around the world to promote healthy eating and physical activity among children. 'The accumulated evidence linking overweight and obesity with cancer is largely based on adult studies,' said Professor Hill. 'But healthy lifelong habits are best established in early childhood.'

This view was backed by Professor Kathy Pritchard-Jones (Sutton, UK), President of the European Society for Paediatric Oncology (SIOPE): 'While it should be stressed that improving lifestyle choices in childhood almost certainly does NOT reduce your risk of childhood cancer, which is, in any case, remote, childhood is the time when the habits of a lifetime are established. So if you want healthy adults you have to start by making healthy children.

'The chronic risk factors for cancer in adults, such as smoking, obesity and diet, are habits that are established in childhood. If we don't do something about tackling how much exercise our young people take and how concerned they are about what they eat and their weight, we are going to have another explosion of cancers, to which unhealthy lifestyles will be a significant, contributory factor. We have just started to make an impact on the rates of cancers caused by smoking, at least in the Western world, but now we are going to start seeing a rise in the rates of obesity-related cancers.'



World Cancer Day marked the start of a year-long campaign to encourage parents, teachers, health professionals and decision-makers to promote healthy eating and physical activity among children.

Aspirin 'cuts gastric cancer risk'

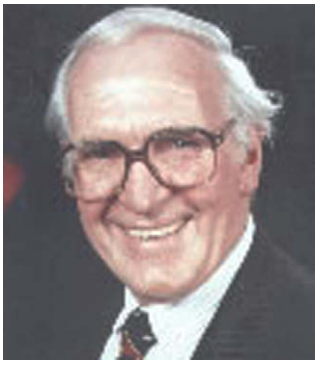
Aspirin users are 36% less likely to develop non-cardia gastric cancer than non-users, US researchers say. Other types of non-steroidal anti-inflammatory drugs (NSAIDS) were associated with a 32% decrease in risk (*BJC* 2009;**100**:551–7).

In a study of 300,000 people, those who had taken aspirin at least once in the previous year had a significant reduction in their risk of this type of stomach cancer. However, in contrast to findings from previous studies, aspirin did not protect against cancers of the oesophagus or cardia.

Lead author Dr. Christian Abnet (NCI, Bethesda, USA) said, 'We found that the risk of non-cardia stomach cancer was lower in people who had taken aspirin, and this risk lowered the more regularly they took it.'

PODIUM

The need for a new framework in drug development



Professor Sir James Black (King's College, London, UK) developed the first clinically useful beta blocker, propranolol, in 1964, and then went on to characterise a new group of histamine receptors and to develop cimetidine, the first clinically useful H2 blocker. He was awarded the Nobel Prize in 1988. Now in his 80s, Sir James is working on a new approach to pancreatic cancer and here, he shares his concerns about the organisation and funding of drug development.

You have suggested we're entering an era of consensus science?

The projects likely to receive funding are already underway, involve large groups of people, and can provide pages of published material in support of the application. Safe science! It's thought to be too risky to fund individuals. But it means that only well-tried horses receive backing. Worse than that, decisions are made prospectively. Candidates have to set out in detail what they think they will do if their application is successful.

Surely there is sense in asking applicants what they intend to do?

While on a grant awarding committee, I received an application for a 5 year grant in which not a single reference was more than 3 years old. It was obvious that the applicant would, quite properly, be knocked off course the day after he got the grant. A scientist's plans for his next experiments have to allow for the results of experiments published by others world-wide. So scientists can only be judged effectively by their track-record, by their proven productivity.

How could retrospective funding work?

The MRC used to have a number of units which were funded retrospectively. When a grant came up for renewal, members of the grants committee would appear on site and ask not, *What are you going to do?* but rather, *What have you done?* We were betting on experience and results.

Today, the heads of big university research groups could apply for grants to work in a particular area. These people have proven track records, they do not need to specify precisely what they will do – they do not know themselves! The grant would then be renewed according to how the first few years had gone.

Is the current system limiting the scope of research?

The projects which tick all the boxes today tend to be based on acquired biochemical and genetic knowledge aimed at rapid technology-transference from lab to clinic. Investors are looking to put in funding for 3 years, and get a utility out of it. Unfortunately for investors, efficient technology transfer can not be expected to come quickly. I have been working on a couple of projects for years – one for gastrin, another for adrenaline. On gastrin – absolutely nothing of commercial value has come out of over 100 years of investment in research but I think that my project is now ripe for exploration. On the contrary, anti-adrenaline drugs have been a rich mine for commercial exploitation for 50 years and look to me to be ready for a new field of exploration – beat2 receptor antagonists. I'm trying to persuade people of the enormous utility of these potentially new products, but they seem to go against current thinking in the pharmaceutical industry.

You're sceptical about the value of High Throughput Screening of huge chemical data bases?

My experience was with natural molecules of known physiological importance. Their activity was assessed using intact-tissue bioassays in vitro. I worked with medicinal chemists, who adapted them. We would build a structure–activity picture, and eventually make a new molecule that seemed to express our objective which in my case was usually a simple competitive antagonist. While there has been huge progress in the current fashions of molecular biology and genetics there has also been much progress in medicinal chemistry. The development of molecular modelling based on molecular fields rather than structures and bench syntheses based on microflow chemistry are not recognised in Big Pharma.

You've said that astute businessmen could rescue the science of new drug invention?

I've also said there are real impediments to how well entrepreneurs and scientists, with their fundamentally different urges and aspirations, can understand each other! But I can envisage a new type of business consultant, setting up a network of academic scouts, and building trust and understanding between commerce and academic science. Post docs often work on what they can get paid to do, rather than what they really want to do. We should be trying to find these frustrated people who are harbouring innovative ideas – and funding them. We need the equivalent of professional football scouts to identify these people, usually frustrated academics, and bring them to the industrial research managers. These academic scouts would not necessarily be high-flying academics but they would know the kind of people industry should be looking for. From my experience of talking to post-docs I know that these people exist.

Helen Saul