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International Cancer News

From the Globe

Can the US-FDA Really Speed Up in Approving New Drugs?

For many years, it has been a common complaint of American oncologists (and patients), that the Food and Drug Agency (FDA) in Washington, District of Columbia, U.S.A. complicates and delays the availability of new anticancer agents compared with their European and Japanese counterparts. The widely used anti-oestrogen tamoxifen was marketed in the United Kingdom and many other European countries years ahead of the U.S.A., and the well-established anthracycline, epirubicin, which is widely used in malignant lymphomas, sarcomas and breast cancer as well as high-dose chemotherapy trials, was only recently approved by the FDA.

However, during the last few years, things have changed. A recent press release by the FDA reported in *The Clinical Cancer Letter* tries to convince the U.S. public, that "Americans today can often buy vital new drugs faster than people in Europe and Japan". A study showed that Americans could buy virtually every vital drug sold in the rest of the world, but had been spared two products, accepted first by England, but then later removed from the market (one drug for schizophrenia and one for aplastic anaemia).

The survey apparently found that Americans had access to five anti-HIV drugs ahead of every other country in the world, and were able to obtain paclitaxel (Taxol®) one year earlier than Europeans. The FDA's commissioner, Dr David Kessler, was quoted to state that "if there is a drug lag, it is not with us in America".

The FDA annual report to the U.S. Congress in December 1995 showed that in the fiscal year of 1994, the agency approved 93% of all drugs within a year of the drug companies' applications. However, the American Pharmaceutical Research and Manufacturers Association presented a slightly different picture: it stated that the FDA approved 150 new drugs between 1990 and 1994, but 60% of those had first been approved in a foreign country (typically, foreign-based companies first seek approval in their home country).

The FDA study found that the FDA-USA and the United Kingdom's drug regulatory agency both approved 58 drugs between 1990 and 1994, 30 of which were first approved in the U.S.A., and 28 of which were first approved in the U.K.

Currently, the U.S.A. has access to 18 drugs which are not available in the U.K. Nine of these drugs are termed "vital drugs", and include the world's only effective drug against Alzheimer's disease. In the U.K., 27 drugs are available which are not licenced in the U.S.A., although these are virtually identical to their U.S.A. competitor drug. Of the 44 drugs approved by the FDA and Germany, 36 of these were approved initially in the U.S.A. Currently, the Germans can obtain 34 drugs which are not available in the U.S.A., and there are a further 32 drugs available in the U.S.A. which cannot be obtained in Germany.

It will be interesting to monitor how the "drug regulatory race" will be influenced by the new European Medicine Evaluation Agency (EMEA) in London, U.K. and the New Drug Development Office (NDDO) of the EORTC in Amsterdam, The Netherlands.

However, drug regulatory decisions do not necessarily influence the efficiency and quality of medical care in a given country or continent, as they would have to be linked with outcome figures such as survival data and (mostly unavailable) data on quality of life and cost benefit ratios.

Hans-Jörg Senn
St Gallen, Switzerland

IARC Evaluates Carcinogenic Risk Associated With Tamoxifen

A working group of 17 scientists from 8 countries met at the International Agency for Research on Cancer (IARC) in Lyon between 13–20 February 1996 to review the evidence on the potential carcinogenicity of a number of pharmaceutical agents. The Working Group was chaired by Dr George Lucier of the U.S. National Institute of Environmental Health Sciences and Dr Anthony B. Miller from the University of Toronto, Canada. The results will be published as Volume 66 of the IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. This series is recognised internationally as providing unbiased evaluations of chemicals, pharmaceutical agents, complex mixtures, industrial processes and biological and physical agents that could increase the risk of cancer in humans. This process is essentially an identification of carcinogenic hazards and is not intended as a basis for risk-benefit determinations, nor for regulatory actions.

Among the agents considered at this meeting was tamoxifen, included for evaluation because of reports indicating a potential hazard in increasing the risk of endometrial cancer. Tamoxifen is recognised as an effective drug for the treatment of breast cancer. It is one of a small group of pharmaceuticals recognised by the World Health Organisation as an essential drug for the treatment of this disease. It is currently being evaluated in a number of chemoprevention trials to determine whether it reduces the incidence of breast cancer in otherwise healthy women judged to be at increased risk of developing breast cancer.

The Working Group reviewed all the published scientific data on second primary tumours reported in patients who had been treated with tamoxifen for breast cancer. The group

further assessed the evidence of carcinogenic effects of tamoxifen in experimental animals, and evaluated possible biological mechanisms of carcinogenesis. As none of these reports were regarded as conclusive on their own, it was the totality of the evidence that had to be considered by the Working Group in reaching their final evaluation.

Two major conclusions resulted from the evaluation process. First, there was consensus that there is conclusive evidence that tamoxifen reduces the risk of centralised breast cancer, i.e. the occurrence of a second cancer in the other breast. The second conclusion was that there is sufficient evidence in humans of the carcinogenicity of tamoxifen in increasing the risk of endometrial cancer, i.e. a tumour originating from the inner lining of the uterus. In addition, the Working Group concluded that there is inadequate evidence in humans that tamoxifen affects the risk of other cancers.

In commenting on these conclusions of the Working Group, Dr Paul Kleihues, Director of the International Agency for Research on Cancer, said: "Breast cancer constitutes a major threat to women's health world-wide. I am very pleased that in spite of the intense interest that this evaluation of tamoxifen has engendered in the medical and scientific community, the members of the Working Group have conducted their evaluation in accordance with the highest standards of unbiased scientific integrity".

It is important to recognise that the findings of the Working Group do not invalidate the conclusions by clinical oncologists and surgeons that tamoxifen is a very important drug which substantially increases the survival of patients with breast cancer. No woman being treated for breast cancer should have her treatment stopped because of the conclusions of the Working Group. The risk of endometrial cancer is far lower than the benefits women with breast cancer receive from tamoxifen. However, it is important that women have access to scientific opinions on the low risk of endometrial cancer, so that they can make an informed decision on the treatment they will accept.

From Europe

The Intergovernmental Conference—1996: FECS's Response

The last Intergovernmental Conference (IGC), held in Maastricht in February 1992, saw agreement on the Treaty on European Community (Maastricht Treaty) although the Treaty itself was not actually ratified by the then 12 Member States until nearly a year later. The IGC in 1996 represents the next stage of European development with a review of the present Treaties, including progress towards economic and monetary union. This could mean at one end of the spectrum that we move closer to a Europe of federal states or, at the other end, that certain powers or competencies of the European Union (EU) are "returned" to Member States and that more decisions are taken between national government, without the involvement of the institutions of the EU.

A reflection group has been set up with representatives of the governments of each Member State under Spain's European Affairs Minister, Carlos Westendorp. It met for the first time in June of last year but the entire process is not likely to be completed until early or mid-1997, when agreement will have to be reached on specific amendments to the European treaties.

Although the IGC discussions will continue over a period of time, many organisations are already producing responses with the aim of influencing the opinions of members of their national governments, as well as Members of the European Parliament (MEPs) and senior European Commission (EC) officials before they decide on their position in the negotiations. It is important, therefore, that the clinical and experimental oncology and cancer nursing community issues a clear line on any points it wants to see taken into account in the discussions as well as reiterating any issues that have already been raised but not acted upon. The response will be used:

- as a lobbying tool at the European and national level to ensure that no decisions are supported by governments that would be detrimental to the clinical and experimental oncology and cancer nursing community, and to inform them of any positive steps these individuals would like to see taken;
- to raise the profile of the clinical and experimental oncology and cancer nursing community *vis-a-vis* European institutions and demonstrate its interest in and understanding of major European developments.

FECS, in accordance with its agreed new role, has prepared a response for the IGC following consultation with its full members. This response makes known the views of FECS on those issues that are of general and specific interest to the membership it serves. These include support for the EC's concern for "ensuring a high level of human health protection" for the citizens of the Member States; welcoming the inclusion of Article 129 in the Maastricht Treaty giving the EC a new competence in public health; and the continuation of the EC's "Europe Against Cancer" Programme. At the same time, the response identifies several areas where further work is required if the "high level of human health protection" mentioned above is to be achieved—notably the need to define more clearly what Article 129 means by "prevention" and "health scourges"; appoint a senior member of the EC with specific responsibility for health; become more receptive to the issues that are important to the clinical and experimental oncology and cancer nursing community; phase out its continued subsidies to tobacco farmers; and review the legislation on the free movement and mutual recognition of qualifications of the health care professions.

The response has been forwarded to key MEPs such as Ken Collins, Chairman of the European Parliament's Committee on the Environment, Public Health and Consumer Protection, and senior members of the EC such as Joao de Deus Piheiro, Commissioner with responsibility for the IGC, and Padrig Flynn and William Hunter, Commissioner with responsibility for the Public Health Unit and Director of the Public Health Unit, respectively.

Copies of the complete response in English are available on request from the FECS office at 83 Avenue E Mounier, B-1200 Brussels (Tel +32 2 775 0207; Fax +32 2 775 0200).

A. Phylip Pritchard
Chief Administrator, FECS

European Multicentre Trial in Multiple Myeloma Starts in Ulm: Tandem HDCT With Autologus Haematopoietic Support

The value of dose-intensive treatment as first-line management of patients with advanced multiple myeloma is under

considerable dispute. In some major trials, response duration has been significantly improved following high-dose therapy over that observed with conventional treatment. Patients who undergo a "tandem procedure" enjoy additional benefit in terms of disease-free survival. Overall survival appears to be clearly superior only in patients who are refractory to conventional treatment such as VAD, as disease relapse after high-dose therapy is often associated with poor response to salvage regimens. One reason for this may be inadvertent reinfusion of myeloma progenitors, selected to high-level chemoresistance by prior induction treatment. Depletion of neoplastic contaminants from apheresis preparations by several log orders may enhance the disease-free survival benefit and alter Gompertzian-type growth behaviour of the tumour, thus granting a net survival advantage. To clarify the value of tumour cell depletion, two strategies may be adopted:

- Conduct a large randomised trial in which the outcome of patients receiving manipulated PBSC is compared to that of patients whose haematopoietic rescue is effected by the unmodified apheresis product.
- Introduce a marker gene into the potential contaminants in the PBSC preparation and identify marked myeloma cells at relapse. Reliable *ex vivo* marking procedures are now well established.

Recently, in the Cancer Centre at the University Medical School in Ulm, Germany, a new European Multicentre Trial, open to new participants, was started for myeloma patients with no or only a brief history of conventional chemotherapy (less than four cycles) that combines both approaches. The induction chemotherapy consists of two cycles of epirubicin, ifosphamide and dexamethasone. PBSC are mobilised with a third cycle of the same regimen, or in the case of progressive disease, with high-dose cyclophosphamide followed by filgrastim. At least 6×10^6 $CD34^+$ are necessary for performing the "tandem approach".

High-dose therapy is then performed according to the Little-Rock protocol: melphalan 200 mg/m^2 for course 1, followed in 70–84 days by course 2: total body irradiation/melphalan 140 mg/m^2. Thereafter, patients receive haematopoietic rescue with either immunoselected CD34+ cells (group A) or with unmanipulated apheresis product (group B). Interferon-alpha is given as a maintenance treatment until clinical progression.

Molecular disease monitoring will encompass detection of clonotypic gene arrangement and analysis of marker gene expression in cells expressing clonotypic immunoglobulins. Participation in gene marking is encouraged for centres with appropriate facilities, legislation and ethical approval, but is not a prerequisite. Accrual of sufficient patient numbers is crucial for valid clinical analysis and the impact of findings. A total of 80 fully evaluable patients per treatment arm is the current aim, but this could be expanded in case of optimal enrolment.

For further information contact: Professor Dr F. Herrmann, Department of Haematology/Oncology, Medizinische Universitatsklinik, Robert-Koch-Strasse 8, D-89081 Ulm, Germany. Fax +49 731 502 4493.

From the Countries

Switzerland

"Giant Marriage" in Basel: CIBA and SANDOZ Merge to Form NOVARTIS

It was a complete surprise to the business and medical world, when officials of CIBA and SANDOZ announced on 8 March 1996 their giant merger to the public. With combined stock-exchange quotations of 76 billion Swiss Francs (64 billion U.S. Dollars) this represents the largest merger in world business history, clearly surpassing the recent mergers of Glaxo-Wellcome and of the Bank of Tokyo with the Mitsubishi Bank in 1995.

If this intended merger is sanctioned by the European Commission and the respective U.S. anti-trust agency (since CIBA and SANDOZ are heavily engaged on a global scale), the new company NOVARTIS will be number one on the global agrochemical and two on the global pharmaceutical market, holding 4.4% of the world's drug sales, according to a CIBA spokesperson at the Basel press conference.

Oncology (especially endocrinological research and the development of MDR-modulators) together with transplantation-immunology and four other major medical fields be the "strongholds" of NOVARTIS, which has promised to the local and federal authorities to keep its central administration in Basel, Switzerland.

Sadly, the merger will mean the loss of 3500 jobs in that small city and a further 6500 worldwide.

Pharmaceutical companies seem to think they have found a miracle drug to cure their own ills in these giant mergers: a growing ecological and antichemical philosophy in society; rising costs of drug research and development; increased use of less expensive generics; political measures to curb drug sales and thus profits; etc. Experienced analysts therefore predict more such spectacular pharma mergers in the near future—a kind of commercial Darwinism. As Richard Posner, a famous economist, summarises it: "In competitive markets, a sustained commitment to any goal other than profitability will result in the firm shrinking, quite possibly, to nothing".

Clearly, all companies must be able to take steps to secure their future business, and these will sometimes be radical. However, it is becoming increasingly apparent that where the social consequences are substantial, companies will be under great pressure to take these into account.

Hans-Jörg Senn
St Gallen, Switzerland

Apology

The publisher apologises to Gwendoline M. Kiebert for the omission of her name under the News item **Quality of Life Around the Globe** published in the *European Journal of Cancer*, Vol. 31A, Nos 13/14, 1995, pp. 2129–2130.

Quality of Life Around the Globe

Measuring quality of life as an outcome measure in health care is gaining momentum both in clinical trials and in clinical practice. Since this is a relatively new field of research, the need for professional exchanges between scientists active in this field is both greatly needed and warranted. It is for this reason that the International Society for Quality of Life

Research (ISOQOL) was created in Brussels in the early spring of 1994. Last month, from October 14–17, this international association held its second meeting in Montreal, Canada. The conference was attended by more than 300 participants from countries all over the world, exceeding the expectation and for some sessions, the capacity of the location. Although sitting on the floor or standing in the corridor might not be the most pleasurable position, the diversity of subjects and the quality of the presentations compensated for this inconvenience. The aim of this scientific international association is to promote progress of the research related to the functional, psychological, and socio-economic repercussions of disease and its treatment. Although the society does not restrict itself to the scientific research of quality of life issues related to a specific disease, cancer always has and still receives major attention in this field, and not without reason. Oncological treatments can cause considerable side-effects in terms of morbidity, and cure is seldom guaranteed. In clinical practice, both the expected gains and losses have to be balanced against each other. Since survival or life-expectancy is often an unsatisfactory measure of outcome, quality of life has become an important issue in oncology. This was also reflected in the programme of the conference, with cancer receiving more attention than any other disease.

During the conference, various areas of quality of life research were addressed. Main topics included ethical and life span issues, determinants of quality of life, new measures, translation and valuation work on existing instruments, clinical studies, and health economics. The emphasis in this conference on cross-cultural differences was striking. For the first time in the short history of quality of life conferences, this subject was a very important issue and the most innovative issue to be discussed. Quality of life research has been developed and performed in mainly western societies. Although quality of life research in developing countries is still in its infancy, there is a growing interest in this issue and the number of studies that perform descriptive comparisons across cultures is rapidly growing.

However, as was apparent from the many oral and poster presentations, there are major cultural differences in the approach to disease and treatment, and therefore, before any instrument can be applied in quality of life evaluations, it has to be validated and tested within each country.

The message is also important for clinical cancer studies that are conducted in Europe. Although there is a long and strong history of co-operation with regard to the conduct of international clinical trials, there are also important cultural differences between the various countries in their approach to communication with and perceptions of patients on cancer issues. An appropriate measurement of the impact of disease and treatment on the quality of life ought to take into consideration the cultural background of patients and physicians.

Gwendoline M. Kiebert
Brussels, Belgium