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Point of View

Drug Evaluation and Approval in the European Community

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FROM January 1995 to 1998, a new evaluation and approval process is to be implemented gradually in the European Community (EC). This process might very well affect the practice of oncology in Europe, as it postulates common concepts and generally accepted therapeutic procedures for the EC. Nevertheless, the process of approval of antineoplastic agents (ANA) in different countries of the EC and the U.S.A. over the last 35 years shows that, despite national approaches of evaluation, very similar results were achieved in the number of available ANA [1]. The idea of common evaluation procedures in the EC was reasonable, but the variability of SPCs in these different countries indicated the potential problems.

PHILOSOPHY OF DRUG EVALUATION IN EUROPE

Classification of the developing agents into three categories

Truly innovating agents. This encompasses biotechnology products and some new chemical entities. For these agents, no prior regulatory experience or previous evaluation exists, and expertise is mostly found among institutional researchers and in pharmaceutical companies. Furthermore, it is anticipated that the majority of true therapeutic advances will be found in this category. Thus, the evaluation should be based upon recognised external experts (as opposed to medical assessors in the National Drug Agencies). Similarly, if a consensus exists on the indications, the safety profile and the Summary of Product Characteristics (SPC), it should be applied without alteration or delay in each country of the EC. This forms the basis of the *Centralised Procedure.*

New chemical entities. The majority of new therapeutic agents would be in this category, as defined from known mechanisms of action, evolution of pharmacological classes and families, or well-known methodology of the study to be conducted. The efforts which have lead to standardisation of preclinical evaluation (toxicology, mutagenicity, teratogenicity), pharmacokinetics, evaluation of side-effects, definition of surrogate and main endpoints and clinical benefit, support the concept that the evaluation of such agents should not differ significantly from one drug agency to another, thus supporting *Mutual Recognition* among members of the EC. This forms the basis of the *Decentralised Procedure.*

National market products. This encompasses agents meant only for a regional or national usage. In principle, these agents are the survivors of 'antique' medical practice and should progressively disappear. For these agents, the evaluation is conducted by a National Drug Agency and no extension of the Assessment to other countries of the EC is considered.

Evaluation of anticancer and related agents

It should be stressed that thus far, these agents have accounted for only a minority of the Medicinal Products evaluated both by National Drug Agencies or by the Commission for Proprietary Medicinal Products (CPMP): no more than 50–60 different chemical entities are currently approved. When approved indications in the EC are examined, wide discrepancies exist both in the approved indications, doses and schedules, and wording of the SPC. It is obvious that the National Agencies have often a limited experience with those agents. Only a minority of them have based their previous assessments on an external evaluation conducted by experts in oncology. The French Drug Agency has set up an Oncology Advisory Board, but appears to be the only Drug Agency in Europe where evaluation is also based on assessment by external experts. Finally, the published Guidelines (1988) are still submitted for discussion in the different agencies.

THE EVALUATION PROCESSES

They are conducted both by the European and National Agencies as summarised in Table 1.

The European Agency (Directive 2309/93)

This controls the co-ordination of the scientific resources made available by competent authorities of the member states for the evaluation and control of medicinal products. It is responsible for: (1) advising pharmaceutical firms; (2) providing information to the general public and professionals; (3) providing scientific and technical support at an international level; (4) co-ordinating the control of Good Laboratory Practice; (5) co-ordinating pharmacovigilance; (6) ensuring the scientific evaluation of the quality, safety and efficacy for Marketing Authorisation Applications (MAA); (7) assessing

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Table 1. Characteristics of European registration procedures for new medicinal products

Procedure	Centralised	Decentralised	National
Agents	Biotechnology products (mandatory) and NCE (optional: high-technology)	NCE (innovative agents)	Regional, local products
Evaluation	External, European	National then mutual recognition	National
Marketing Authorisation Applications (MAA)	European, binding	National, but common wording	National

reports, SPCs, directions for use and labelling. Thus, the European Agency is active in the Centralised Procedure, the Decentralised Procedure (appeal) and pharmacovigilance. Scientific support is provided by European experts and by the expertise of national agencies.

The Centralised Procedure

This procedure is intended to supply international expertise to innovative agents. Once the MAA is submitted to the CPMP, evaluation (Parts I and II, Parts I, III and IV) will be conducted by one rapporteur and one co-rapporteur nominated by the CPMP. Such evaluation has to be conducted within 210 days and should rely upon external experts. If the opinion of the CPMP is positive, a report on the assessment and the reasoned conclusion will be transmitted within 30 days so that a Draft Commission Decision can be proposed. Each member state can then transmit detailed opposition to the CPMP. If no opposition is encountered, it will be the responsibility of the Standing Committee to approve the draft and to promote the Commission's Decision leading to publication in official journals of the EC. If the opinion of the CPMP is negative, the applicant should indicate its intention to appeal within 15 days and present this appeal within 60 days. The new elements are then submitted to the CPMP; if a negative opinion is maintained, it can be rejected by the Standing Committee following a vote. If there are no positive or negative views, the dossier is blocked.

The Decentralised Procedure

Such a procedure, which relies upon mutual recognition, is essentially meant for those agents where experience already exists in the E.C. The applicant has to submit the dossier (European Format) to a member state which will become the rapporteur state: the evaluation will be conducted by the national drug agency, and the conclusion (opinion, assessment report, SPC, package leaflet) will be transmitted with Part I of the dossier to the other agencies. Member states should then, within 90 days, either agree with these conclusions or appeal (to the CPMP). In case of appeal, the CPMP becomes active as previously seen for the Centralised Procedure.

EXPERIENCE WITH THE EUROPEAN PROCEDURES

Very little experience exists so far. Almost all the biotechnology agents (Interferons, haemopoieteic growth factors, interleukin 2) were assessed through the former Concertation Procedure) as was the case for paclitaxel. A number of recent cytotoxics have been registered through National Procedures. The first agent to follow the Centralised Procedure has been docetaxel. Indeed, it appears that some of the questions raised by some National Delegates were associated with limited experience in the field of anticancer agents. As far as the Decentralised Procedure is concerned, no experience is available thus far.

Among the potential problems are the following.

(1) Strong feeling among oncologists that early availability of new agents, followed by in-depth evaluation conducted by multidisciplinary study groups is the strategy which will offer the fastest and strongest guarantee to cancer patients. One can point to the fact that the ultimate benefit of some agents—such as improved cure rates in node-positive breast cancer due to anthracycline-based adjuvant therapy–was demonstrated more than 15–20 years after MAA was obtained.

(2) Different expectations from the agencies and the oncologists: the latter will obviously accept data from Phase II studies provided that they show adequately a valid level of activity (usually based on Response Rate in a representative population of patients) to further define use of the agent mostly in combination regimens.

(3) Different evaluation of side-effects: oncologists will not usually consider severe neutropenia of short duration as a truly dose-limiting toxicity as it can be limited by haemopoietic growth factors, the use of which should not be considered with investigational agents. Similarly, other side-effects, such as drug-induced emesis, alopecia, sensitive neuropathy, are usual side-effects of some widely used cytotoxics and are not considered as dose-limiting by most oncologists.

(4) Different estimation of the weight to be given to some criteria, such as quality of life, in the evaluation of a new agent.

It is clear that in the rapid evolution of cancer therapy, the expertise of oncologists dedictated to drug evaluation as well as to evaluation of new therapeutic approaches (intensive chemotherapy, cell therapy, etc.) can improve the evaluation of antineoplastic agents. The experience of the agencies where an advistory board exists (France, U.S.A., Canada) tend to demonstrate improved evaluation without discrepancies between internal assessors and external experts. It is hoped that the experience gained with the European Procedures in the field of antineoplastic agents will rely more heavily on European experts and allow the best and quickest possible evaluation of these agents in Europe.

1. Brown JS, Bienz-Tadmor B, Lasagna I. Availability of anticancer drugs in the United States, Europe, and Japan from 1960 to 1991. *Clin Pharmacol Ther* 1995, **58**, 243–256.