

## Position Paper

### PROPOSAL FOR A REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL ON MEDICINAL PRODUCTS FOR PAEDIATRIC USE AND AMENDING COUNCIL REGULATION COUNCIL REGULATION (EEC) N° 1768.92, DIRECTIVE 2001/83/EC AND REGULATION (EC) N° 726/2004

#### [A] Introduction

In many member states in Europe, national paediatric oncology organisations promote the care of children with cancer. These national organisations interrelate through a number of networks, initiatives and clinical trial collaborations. SIOP Europe is the pan European organisation which exists to promote the overall needs of the paediatric oncology community in Europe.

Paediatric oncologists are very much aware of the shortcomings of current legislation relating to drugs used in paediatric practice. The principal issues in relation to existing medications include:

- **Out-of label use:** Many of the drugs used for the treatment of children with cancer, despite being well established in clinical practice, are not appropriately authorised for use in children and adolescents. For example, in one recent study of children treated for acute lymphoblastic leukaemia, unlicensed preparations were used in 40% of prescriptions for chemotherapy, due to a lack of approved formulations suitable for the paediatric patient.

- **Lack of commercially available paediatric formulations:** Paediatric oncologists regularly encounter difficulty with the formulation of some products intended for oral administration, resulting in inaccurate and or complex dosing schedules, and, in some cases, precluding the use of certain agents in very young children altogether.

- **Withdrawal from the market of formulations used by paediatric oncologists:**

Some formulations available and in clinical use for many years are now being withdrawn by some manufacturers who have, so far, been unwilling to engage with the implications of such decisions on the care of children. Although these formulations are no longer patent protected, even generic companies are unlikely to market formulations withdrawn by originator companies due to lack of commercial interest.

## **[B]Comments on the draft Regulation on medicinal products for paediatric use**

In terms of new drug development, we are conscious that pharmaceutical companies are reluctant to support studies to evaluate new cancer chemotherapy drugs for use in children. This stance is taken principally on economic grounds, but also because of the legal, administrative and ethical challenges of conducting clinical trials in children. Moreover, the advent of new, biologically targeted agents is likely to heighten the need to develop some new anti-cancer drugs as orphan drugs, even for use in adult cancer. This situation will further limit the paediatric development of new drugs in the absence of new incentives.

We therefore welcome the Commission's draft proposal for a regulation on medicinal products for paediatric use and would like to make the following comments on the proposals:

1. We believe that the establishment of a Paediatric Board is a sensible strategy as this will provide an important interface between the views of professionals, parents / patients, regulatory authorities and the pharmaceutical industry to implement the procedures required to establish and evaluate paediatric investigation plans and marketing authorisations. Because of the strong relevance of the work of the Paediatric Board to paediatric oncologists, we urge that at least one professional member of the board is a paediatric oncologist.
2. We support the concept of incentives as well as obligations for pharmaceutical companies and are aware that a similar approach in the United States has improved access to medicinal products in children. We are however concerned that the current proposal could mainly stimulate paediatric development of new and/or still patent protected drugs, with little influence on the status of drugs which are unlicensed and no longer covered by patent or supplementary protection.

In particular there should be a clear commitment to the Community paediatric study programme (MICE), which was previously described under Art 22 and is now only referenced under "justification". It is important that information is made available about how the programme will be designed, with which partners it will be established, when it would come into action, and how it would be funded. We believe that this programme is essential to ensure the overall ability of the paediatric regulation to deliver its intended benefits.

3. Although particular attention is paid in the proposal to the incentives and obligations which may assist the paediatric marketing of newer drugs, we strongly believe that there must be a more robust approach to the status of drugs that are unlicensed and out of patent. Many such agents have been used for so long in children that there is already

substantial knowledge gained from regular clinical practice. Furthermore, there are data from previous clinical trials which, providing an assessment of quality is satisfactory, could be a very valuable source of additional data. As it is difficult to see pharmaceutical companies becoming willing to study drugs which are already well established in therapy, and it could be argued that this may not be an appropriate use of resource, we recommend that the procedures to be established for agreeing a paediatric investigation plan should include the ability to assess historical data (as briefly mentioned under whereas 19) without the requirement for new studies in all circumstances. Therefore a paediatric investigation plan should not only be prospective, but should also consider data based on existing studies and bibliographic evidence as appropriate.

4. The concept (in Article 43) of the development of a European network is of particular interest to the paediatric oncology community which has already well established networks which must be taken into consideration. The link, if any, between the paediatric study programme and the European Network is not identified and the Network should in no way replace existing clinical trials networks.

There is a strong tradition of academic (i.e. non pharma supported) clinical trial activity in paediatric oncology and, in striking contrast to the current position in adult cancer care, the great majority of children with cancer in existing EU member states are treated within a clinical trial framework. The majority of these trials involve international collaboration, many are now pan European and, increasingly, some collaborate with countries outside Europe. We believe that paediatric oncology is advanced in relation to many other areas of paediatric clinical practice in this context yet, despite the expertise available and the excellent professional collaboration that exists within the paediatric oncology community in Europe, it is proving increasingly difficult to identify the resources necessary to undertake the collaborative international studies required for the evaluation of new therapies. The requirements of the Directive 2001/20/EC (so-called the Clinical Trial Directive) is adding extra demands (financial and organisational) in terms of the standards to which such studies must operate. It is clear therefore that the effective implementation of appropriate clinical research network(s), as suggested in this proposal, will require resource investment. This must be considered and quantified.

5. The new regulations should incorporate measures which will particularly support the expectation of paediatricians in the new EC countries to be able to participate in the development of new cancer treatment and to benefit from advances already made in the care of children and young people with cancer in the existing EC countries. Have the implications of the expanded EU been adequately considered in assessing the resources required for infrastructure and network support?

6. It is clear that collecting new paediatric data will have a cost, which will be further increased by the new requirements from the Clinical Trial Directive. Where the incentive is adequate for the Industry, the cost will be mainly or totally supported by the Industry. However, the draft Regulation is disappointing in its assessment and commitment to fund

independent research in paediatric clinical trials. First, it implies that the paediatric study programme (MICE) will be limited to old products not covered by patent. This means that independent research on patented and marketed drugs is *a priori* excluded from the Community programme. Second, no funding is yet planned either for the programme or for the European Network. Surprisingly, Article 47" only mentions a special Community contribution just to cover the work of the paediatric committee, the scientific support provided by experts and the agency. We believe that a comprehensive plan to improve paediatric research in Europe must go beyond funding the coordination role of the Agency, and that to leave these aspects entirely to undefined future legislation is inappropriate. It is important to ensure that most of the eventual funding would not be used to fund bureaucratic activities without proper funding of the actual research itself. An assessment of all the necessary investments and of the cost to the Community should be considered in more detail.

### [C] Summary

Paediatric oncologists welcome this initiative but feel that the draft regulation focuses mainly on new drugs and/or drugs still under patent while nothing robust has been foreseen for all the drugs currently used and no longer covered by a patent:

- The PUMA concept is vague,
- The MICE programme is not well defined and no longer under an article (in addition it concerns old products and therefore excludes academic research on patented drugs),
- The funding is considered only for the "administrative" part of the elements to be put in place,
- There is no real guidance for the network.

Overall, the document is very disappointing in its assessment and commitment to fund independent research in paediatric clinical trials.

In this context, FECS and its society of Paediatric Oncology (SIOP Europe) believe that oncology represents an area where paediatric clinical practice has particular skills and experience in international collaboration at a European level and would like to take an active role in the further development of these proposals. Indeed, paediatric oncology could be considered as a 'model system' for such development.

We hope these comments are helpful and will constructively contribute to the final content of this very important legislation.

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