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## SIAR International Conference – October 2005 Scientific Advice and Protocol Assistance: tools for the development of innovative and orphan drugs

In agreement with the other speakers, we have decided to begin this session with a concrete example of "Scientific Advice" to show you immediately all the advantages of this important tool.

In addition to this case report I will shortly discuss the feasibility of a "common development" for innovative drugs and the issue regarding a partially "shared" development vs. the independent assessment in the evaluation of novel drugs.

I suppose that you know the "confidentiality agreement" between the European Commission, the European Agency (EMA) and the US Food and Drug Administration (FDA) accomplished in September 2003. Its primary aim was to "strengthen communication... and reinforce public health promotion and protection".

One priority area was the possibility of "parallel scientific advice".

This agreement, renewed and reinforced in 2005, was expected to "accelerate access of patients to new and innovative medicines" without "creating any kind of legal obligation on the part of the FDA, the European Commission or the EMA."

Immediately after this agreement Dompé had the honour and the privilege to be the first Company to receive "parallel" advice in October 2003. The drug submitted to this new procedure was reparixin, a novel specific inhibitor of IL-8 bio-

logical activity, proved to inhibit the PMN chemo taxis and to prevent reperfusion injury after transplant. The proposed indication was prevention of delay graft function in organ transplant.

Before the "parallel advice procedure" reparixin obtained Orphan drug designation in Europe (September 2001) and in the US (January 2003). Afterwards reparixin was subjected to a European "protocol assistance procedure" having a "pre-submission meeting" in October 2001. During this meeting EMA experts concurred that the phase 1 studies should follow the standard scheme. Thus, the "protocol assistance" was requested for the phase 2 studies in May 2003. Contemporaneously a pre-IND meeting with FDA was organized.

The main topics of the "protocol assistance" are reported in table 1: they concerned mainly the clinical development.

Due to the different role of FDA, which is responsible for the review of INDs submitted by sponsors to permit conduct of CTs in US, the questions to FDA and their answers (table 2) were not superimposable to those of the EMA (table 3).

Needless to say, both groups of suggestions and comments were extremely useful and presently reparixin is evaluated in two double-blind clinical trials: in lung and kidney transplants. The study in lung transplant is being performed in the US and Canada, while the studies in kidney transplant are

Tabella 1 – Reparixin: topics for Protocol Assistance

Reproductive toxicology
Clinical development strategy
Primary end point
Sample size and clinical relevance of the expected difference
Inclusion criteria
Treatment schedule
Immunosuppressive regimen

Tabella 2 – Reparixin: answers from FDA

Requirements to establish an IND
Appropriate selection of studies conducted
Suggestion: in vitro interactions with immunosuppressor and p-glycoprotein
Discussion about the "quantity" of evidence
Primary end point: discussion during IND procedure

Labeling - Repetition - CPMP Scientific Advice

Segment II studies or strict contraindication for MAA  
 Suggestions about the clinical development  
 New agreed primary end point  
 Sample size: stronger degree of statistical significant

being conducted in the US, Italy, France and Spain.

Of course, a "Common Development", if feasible, would be much more valuable than the "Common technical document" because common development concerns the substantial work needed during development whereas the "CTD" is simply a formal way to assemble the documentation.

However a "common" or "global" development is particularly challenging for innovative drugs when regulatory guidelines are not avail-

able and examples from similar drugs are lacking. It is further complicated and more difficult when evaluating an orphan drug, due to the paucity of patients available for study. In these cases, early discussion with Regulatory Agencies can be essential to reduce time and risk during the development.

Finally I wish to emphasize the strong differences between the "scientific advice" procedures and the "assessment" for the approval of drugs:

- SA is issued during development whereas the assessment is perfor-

med at the end of development.

- SA concerns the methodology of the studies whereas the assessment concerns the evaluation of the results.
- SA pertains to the program of development whereas assessment pertains to the results.
- SA is focused on the "know how" (how to measure the benefit/risk) whereas the assessment is focused on the "know if" the benefit/risk is positive.
- SA is in the field of R&D whereas assessment decides the commercialization.

In conclusion, in my opinion, a development program partially shared with the Authorities does not mean a prejudice in the evaluation of the actual results, because the two activities are completely distinguished in terms of time, methodology, subject and targets.