CORRESPONDENCE/

Cetus Commentaries

To the editor:

I would like to clarify various issues raised by the article "Proleukin Slowing the CPMP Merry-Go-Round" (*Bio/Technology* 8:894, Oct. '90). The author—apparently not a supporter of European Community mechanisms for harmonisation and mutual recognition—has let his attitudes affect his portrayal of the regulatory history and current status of Proleukin interleukin-2.

The article implies that there has been a shift in attitude and a withdrawal of support among European authorities, and bases this assertion on the fact that various countries, following the recommendation of the Committee for Proprietary Medicinal Products (CPMP), asked for additional information post-approval. In fact, the inclusion of the CPMP recommendations in individual countries' authorisations is a laudable example of harmonisation at work: These subsequent actions by individual countries reflect CPMP opinions being adopted broadly. To suggest that this may instead foreshadow a revocation of Proleukin approval is misleading.

The CPMP considered the data in the original dossier for Proleukin sufficient to assess the quality of the product and its safety and efficacy in treating metastatic renal cell carcinoma. For regulatory agencies to then require additional information is common. For example, the original dossier recommended two dose/regimen schemes; much of the added information requested by CPMP relates, not surprisingly, to optimum administration of treatment. EuroCetus complied with these requests in a timely manner as required under CPMP procedures. Also, for some authorities to ask for other information—such as subsequent data on long-term survival and teratological effects—is hardly unusual. Nor is the restrictive package insert language recommended by CPMP reason to challenge the product's initial approvability. Such packaging is in line with that for many cancer drugs. And the CPMP recommendation that Proleukin be administered in specialized hospitals with intensive care units is similar to the restrictions imposed on alpha interferon when it entered the market.

We believe that what you have characterised as a controversy over approval merely reflects the normal difficulties one should expect as individual country representatives attempt to define the scope and interpretation of European Community mandates generally and the CPMP procedures in particular. The Danish authorities asked us for answers to questions that were not raised in the initial CPMP question list. The necessity of creating a public law contract between the German regulatory agency and EuroCetus for Proleukin approval, noted by the author, has now been addressed by new amendments to the German drug law, and would not be needed today. Total harmonisation may yet be eluding us, and individual countries inevitably will have differing concerns, but authorities are trying to work constructively with the process.

The CPMP process is relatively new, and even staunch supporters agree that it can be improved. Some believe that the rapporteur should be assigned by the committee and not selected by the company; others see a need for more scientific expertise at the central level. Much can and should be done to enhance the structure and function of the mechanism that has emerged from 87/22.

In conclusion, while mutual recognition may be far from a reality, to characterise the process as a "merry-go-round" is neither constructive nor accurate, nor is it applicable to the approval of Proleukin.

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LaMonica's points are well taken except for the first: Neither Bio/Technology *not the author of the article has an opinion (on the merits of harmonisation) by which to be influenced.*

To the editor:

We would like to clarify several points raised in Douglas McCormick's editorial, "Combination in Restraint of Trade," and an accompanying article, "The Cetus Experience: Troubles with Clinical Trials Design and Data Presentation" (pps. 781 and 815, Sep. '90). We are concerned that some misconceptions about FDA's policies concerning combination and cellular therapies may have been conveyed to the biotechnology community.

A major point of the editorial was that certain regulatory requirements for demonstrating efficacy may not be appropriate for cytokines and other newer agents. In particular, McCormick asserted that "FDA will have difficulty considering any [marketing] application for combined biotherapies unless one of the therapeutics has proven efficacious on its own." This statement reflects a misunderstanding of FDA policies and regulations related to combination regimens.

FDA could, in fact, approve a combination regimen of biological therapies even if no agent in the combination was effective by itself; in fact, the Agency has done so for combination drug therapies. In considering combination therapies, clinical evidence demonstrating that each agent contributed to the efficacy would be required. Such evidence may be demonstrated by clinical trials designed to compare the activity of single agents or combinations. The rationale for this requirement is based on the principle that patients should not be exposed to the known or potential risks of a component of a therapeutic combination unless that component has been shown to be beneficial.

Accordingly, while many caveats about dosing, safety, and other necessary information could be made, this basic point should be clear: single agents do not have to be effective on their own, but for approval of the combination, each component must be shown to contribute to efficacy. Additionally, if the combination of two agents, each efficacious alone, results in superior efficacy, the combination use can be approved.

Both the editorial and the article also address FDA regulation of cellular therapies such as the use of lymphokine activated killer (LAK) cells and may have conveyed the incorrect impression that the Agency has discouraged or is disinterested in the development of such therapies. Moreover, both imply that it is difficult for sponsors to obtain guidance from FDA for conducting cancer trials.

The Agency routinely provides guidance to sponsors in several ways. The FDA has published the document, "Points to Consider in the Collection, Processing, and Testing of *Ex-Vivo*-Acti-