Letter to the Editor

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Dear Sir,

In reply to the letter of Noé and Werner (*Cytotechnology* **26**: 81–82, 1998), we assert that the way we chose to present the ideas in the *batch v. continuous* controversy was intended to stimulate a continuing debate on this issue.

There are two matters of substance in their letter. The first affirms that... 'Nowhere in our publications is it to be found, for example, the statement that the regulatory agency for biologicals in the U.S.A. will not licence products based on processes which operate as fully continuous cultures'. We agree that the above statement does not occur as such, but in the Werner et al. paper¹ on page 64 in describing the use of the Post Production Cell Bank which... 'is used for investigations which give evidence that no change occurred to the cell culture during the long term bioprocess'. The use of the term 'no change' implies the impossibility of conforming with the requirements for validation. A similar statement may be found in the next paragraph where it is claimed that... 'In addition, it has to be demonstrated that the specific productivity (μg protein per 10^6 cells per day) remains constant at different harvests and from bioprocess run to bioprocess run'. Here the use of the term 'remains constant' again implies the impossibility of conforming with a validation requirement. We concluded from these considerations that, in view of the stated requirements, it would be impossible to obtain a license from the regulatory authorities.

The second issue is related to the genetic stability of cells used in continuous culture. We based our statement on the following quotation from the Werner et al. paper on page 54. 'This tendency to genetic inhomogeneity can be enhanced by suboptimal growth conditions or long term bioprocess periods without selection-pressure and can result in genetically unstable populations'. In subsequent sections of their paper they imply that both growth conditions are suboptimal (chemically and physically) and the bioprocess periods are long in the continuous culture application, thus providing the apposite conditions for genetic instability. It would be difficult for us not to conclude that the Werner et al. paper provides clear inferences which lead to the contention that genetic instability was going to be a necessary problem for continuous culture.

¹ Werner RG, Walz G, Noé W and Konrad A (1992) Safety and economic aspects of continuous mammalian cell culture. *J. Biotech.* **22**: 51–68.