Phase II Clinical Trial Results—Too Many Expectations?

To the editor:

There have been a number of upsets in recent months in the biotech sector as phase III clinical trial results have been announced which have not supported promising phase II data. The furor which this has caused within the financial community has helped to wipe 40 percent off the value of biotech stocks and to create a bear market in which many promising development companies now find it extremely difficult to raise much needed funding.

There has been much press comment on the subject of why Xoma, Centocor, and Synergen have all failed to find a cure for septic shock after encouraging early results. Opinions have ranged from the notion that septic shock, being of multiple origins, should not be expected to respond to a single therapeutic agent to the thought that the phase II trials should have been larger and thus more accurate in the first place.

"Why am I always the one who has to stamp 'Created by B & B Labs' on their foreheads?"

This suggest that analysts may not have a thorough understanding of the clinical development process. The fact of the matter is that phase II studies have only limited power to predict a phase III result either from the point of view of efficacy or safety. This limited predictability in phase II trials is not confined to those run by the biopharmaceutical industry. Experienced companies have also stumbled in late clinical trials as the CAST antiarrhythmic study or the Wellcome studies in HIV-positive patients have demonstrated. Any experiment uses a limited sample of a population which, it is hoped, represents that whole population. The larger the size of the experiment, the more typical of the entire population it becomes. The limited size of phase II trials means statistically that they cannot be expected to detect a modest therapeutic effect or a relatively uncommon side effect which may be found with a study of larger sample size. Conversely, random clustering of data in a small trial may give a false positive result which is lost in a larger, more representative study. Other factors which may have a bearing include differences in the patient populations included in large-scale trials, changes in definitions of the endpoints or the techniques used to detect them, and the expansion into many clinics with more heterogeneous medical practices than may occur with a small- scale study.

The notion that these problems can be overcome by doing larger phase II studies misunderstands the purpose of phase II. This is to obtain some feeling about the tolerability of the drug in patients and the adequacy of the chosen dosing regimen before large scale trials are undertaken. But phase II "proves" nothing and, for perfectly good statistical reasons, phase II may well not support phase II. It will not necessarily be because, as some people have suggested, the "wrong" study has been designed for phase III or that the study has been poorly conducted (although these are also possibilities) but simply because the larger studies have exposed the sober truth behind the optimistic illusion.

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More Financial Results

To the editor:

The news item in the April 11 issue (*Bio/Technology* **11**: 426, April) on the 1992 financial results of 82 [*sic*] biopharmaceutical companies lists a number of non-U.S. companies, and it is surprising that two were overlooked.

InterPharm Laboratories, headquartered in Israel, with shares traded over-the-counter in New York, had 1992 sales of $51.597 MM, profits of $6.754 MM, and a sales increase over 1991 of 46.6 percent. These results would have placed InterPharm 12th, 7th, and in the middle of the list, respectively. Sales were mainly human fibroblast beta-interferon, certainly a biopharmaceutical.

Bio-Technology General, headquartered in New York, with major operations in Israel, had 1992 sales of $6.019 MM, a loss of $9.797 MM, and a sales increase of 17.2 per cent, and would have placed in the middle of the list on all counts.

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