

## BIOTECHNOLOGY

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## THE FIRST WORD

### COMBINATION IN RESTRAINT OF TRADE

Or perhaps we should have called this "Combinations restrained from trade."

A few years back, we wound up spending a very late night in a Colorado bar with a UCLA cancer researcher. The man was angry, weeping in enraged frustration at regulators who would not permit combined biotherapies for terminal cancer patients—people who would die, he firmly believed, without imaginative treatments based on the body's own immune response.

That bears on one of the lesser lessons of Cetus's reverses in its maiden appearance before the U.S. Food and Drug Administration. (See the news and feature articles by Mark Ratner in this issue.) The regulatory apparatus—schooled in specifics and simples—is still not philosophically equipped for the complexities of treatment with biological response modifiers.

Now, there are still questions in Cetus's case about who did what, and with which, and to whom, in mapping the studies and submitting the data. It appears, though, that the company was actively dissuaded from filing a Product License Application (PLA) for treating metastatic renal cell carcinoma (RCC, a deadly and refractory cancer) with a combination of interleukin-2 (IL-2) and lymphokine activated killer cells (LAK).

At the showdown, however, FDA made it clear that combined data were not germane to an application involving IL-2 alone. It appears that FDA will have difficulty considering any application for combined biotherapies unless one of the therapeutics has already proven efficacious on its own.

And that's the point that troubles us. The current policy—or attitude, if it is not a formally sanctioned policy—is eminently suited to conventional chemotherapies combined for increased benefit. It is most assuredly not appropriate for treatments by biological response modifiers. Ultimately, as SmithKline Beecham's George Poste and others have repeatedly pointed out, BRMs ought to be administered in a carefully timed sequence, bringing the patient's system to a state in which it responds to the challenge of disease. Omit a step, or perform one out of order, and the net effects drastically diminish—or vanish. It may indeed be impossible to individually demonstrate the efficacy of any one element in such a sequence, while the combination may be extremely potent.

This is one Catch-22 of modern biotechnology. There are others, also in evidence during July's FDA hearings.

According to those in the room at the time, Wall Street's biopharmaceutical analysts apparently huddled and declared Cetus the winner before the gavel even went down. Then, as the meeting wore on, the analysts crept out of the room one by one for cellular phone calls back to the home office—presumably to say things were not going well for the home team. By the end of the meeting, the analyst community was in a chagrined frenzy and calling for executive blood.

Indeed, viewed through the end-of-quarter myopia—the perspective of gamblers who are always hoping that superior insight will fix the game in their favor—Cetus's reversal was a stunning setback. But is money what the game is all about? In the end, the object is to get an effective treatment to people who need it. Cetus has suffered a temporary delay in that goal: It seems apparent that the product will be approved, perhaps before year's end, perhaps a bit later. Those who will suffer most, it seems, are not company management, or the regulators, or the analysts, or the investors, but patients waiting for a demonstrably effective treatment.

In going through the comments for this year's compensation survey (the results are published in this issue), we were struck by the number of industry researchers and research managers exasperated at 1) the short-term horizons of their management, and 2) the almost indecipherable morass of regulation (this was especially true of researchers and research managers working in agriculture, but applied as well to their more numerous colleagues in the pharmaceutical industry). The disappointments of July mirror those frustrations to the life.—Douglas McCormick