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The regulator disapproves

Pressure is mounting on the US Food and Drug Administration (FDA) to explain its decision to ignore an advisory committee's positive recommendation for the cancer vaccine Provenge.

In the coming weeks, it looks increasingly likely that the US Congress will launch an investigation into the circumstances behind the FDA's decision last May to delay approval of Provenge, a recombinant therapeutic vaccine developed by Dendreon for use in terminally ill patients with androgen-independent prostate cancer. Cancer patients have been exasperated by the agency's decision to ignore an advisory committee recommendation made in March, which gave the green light for full approval. The flip-flop came following the panel meeting, after FDA received three letters sharply critical of Provenge's safety and efficacy, which were subsequently leaked to the press. With allegations of 'dirty tricks' by agency officials and undisclosed, potentially damaging corporate ties associated with at least one of the letter writers, the onus is now on the FDA to affirm the legitimacy and impartiality of its regulatory process.

Why did FDA ask Dendreon for additional clinical, chemistry and manufacturing data for Provenge against scientific advice? Certainly, patient groups, denied a 'lifesaving' therapy, would like to know why. And in a field where Provenge represents not only a pioneering technical approach but also the first nontoxic treatment for prostate cancer, investors and the oncology community would like to know why.

Over recent months, pressure has been mounting for an answer. Thousands of letters have purportedly been written to FDA, members of Congress and the Department of Justice. Demonstrations have been held outside FDA's offices. And the prostate cancer patient advocacy group, CareToLive, has filed lawsuits against FDA contesting the decision and demanding access to Provenge. It has even run an ad campaign on buses in the Washington, DC, area critical of the FDA's handling of Provenge.

The signs are that all this is beginning to register on the political radar. In December, three Congressmen—Mike Michaud (D-Maine), Dan Burton (R-Ind.) and Tim Ryan (D-Ohio) —wrote to the House Energy and Commerce Committee citing "ethical violations" and the need for "full disclosure…to restore confidence in the FDA." An inquiry is now expected.

Part of the reason for all the hoopla is that, apart from FDA's decision to ignore scientific advice, there were also several other irregularities in the process.

At least one of the Office of Cellular, Tissue and Gene Therapies Advisory Committee members who voted against Provenge and then wrote to FDA to criticize the approval recommendation—Howard Scher of Memorial Sloan-Kettering Cancer Center—failed to disclose important competing financial interests. Scher is a scientific advisory board member of venture capital firm ProQuest, which owns an 8.3% stake in Novacea, a company that was developing a competing prostate cancer drug, Asentar. Scher also happens to be the lead investigator in Asentar trials.

Curiouser still, an alleged power struggle over the regulatory jurisdiction of cancer vaccines between the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation Research (CBER) has thrown the actions of FDA officials under scrutiny. When Scher and two others sent FDA letters critical of Provenge, these letters were not only mysteriously 'leaked' to an industry newsletter, *The Cancer Letter*, but also supposedly ghost written by someone inside CDER. And during the advisory committee meeting itself, after four panel members had answered "no" when asked whether there was evidence of Provenge's "outright effectiveness" (CDER's preferred wording), CBER director Jesse Goodman changed the phrasing to ask whether there was "substantial evidence" of effectiveness. With the revised wording, the panel voted 13 to 4 in favor of efficacy (the vote for safety was 17 to 0 in favor).

Efficacy is key here because in both Dendreon trials presented to FDA, Provenge failed to meet its primary endpoints. In certain respects, Dendreon shot itself in the foot by setting an over-optimistic efficacy expectation/hazard ratio for the trial of 0.585, which no conventional drug or chemotherapeutic has ever achieved in a comparable setting of late-stage disease. At the same time, however, Provenge did extend median overall survival by 4.5 months, and after 3 years, 34% of the men who received the therapy were still alive, compared with only 11% who received a placebo.

Thus, the trial was not designed to demonstrate survival advantages, but reanalysis showed that it did. Is it right that the FDA should ignore this? In the real world, in a scientifically assessable way, Dendreon's underpowered trials do show real efficacious value, despite clear deficiencies in trial design and execution. And when the sole therapy available to end-stage prostate cancer patients is Taxotere (docetaxel)—which extends survival by only two-and-a-half months and is so toxic it kills 300 patients itself every year—it is easy to understand why patients feel the data were strong enough. And it seems the advisory committee thought so, too.

FDA is, of course, perfectly within its rights to ignore all advice, but it is rare that it does so. The last known case where it overruled an advisory panel recommendation was the 'morning after' contraceptive Plan B. In that instance, the agency was roundly criticized for choosing political expediency over science.

In the case of Provenge, equivocal trial data and malpractice tittle-tattle have created a fog of uncertainty that provides little guidance of any kind to anyone. It may not be within the FDA's statutory remit to orientate clinicians and biotech companies, but the fact is agency decisions do have that effect. And, at present, FDA appears to have neglected its role in guidance because of a knee-jerk defensive response to accusations of process impropriety.

At the very least, FDA should now explain its decision. Those developing other cancer vaccines would welcome the clarity. And prostate cancer patients, denied access to a potentially life-preserving therapy, deserve an answer. Anything less and confidence in the agency's competence to regulate similar experimental cancer therapies could be seriously compromised.