FDA Has Problems, But Too-Fast, Too-Lenient Reviews Aren’t Among Them

By Henry Miller — May 8, 2019

In its international edition on April 25, the New York Times ran a blatantly anti-Semitic political cartoon that portrayed a blind President Trump wearing a yarmulke being led by Israeli Prime Minister Benjamin Netanyahu, who was depicted as a dog wearing a collar with a star of David.

It was, of course, outrageous, and seemed to me symptomatic of the Times’ cluelessness about many things. Putting it another way, its editors, reporters, and columnists often don’t know what they don’t know. (Disclosure: I have both written for the Times and been criticized on its pages.) Take, for example, its coverage of science and medicine, which used to be stunning, the province of reporters who knew their trade and devoted decades to it. Today, however, the paper’s reporters and, especially, their editorial writers often lack a solid grasp of the subjects they cover. For example, an editorial that accused the FDA of reducing its scrutiny of new drugs in development to dangerous levels was inaccurate or misleading in several important respects.

Consider this statement, for example: “The agency now requires fewer and smaller clinical trials, approving some drugs after just one successful trial.” There are good reasons that the clinical testing of new drugs can be accomplished with fewer and smaller trials. We are entering the era of precision, or personalized, medicine, the mantra of which is “the right dose of the right drug for the right patient at the right time.” It reflects that treatments are gradually shifting from a relatively imprecise one-size-fits-all approach to a more personalized one, so that patients can be matched to the best therapy based on their genetic makeup, the specific characteristics of their illness, and other predictive factors. This enables doctors to avoid prescribing a medication that is unlikely to
be effective or that might cause serious side effects in certain patients.

Relevant to the assertion in the *Times*’ editorial, it also enables drug testing to be performed in smaller, better-targeted populations. That is not a completely new concept; under appropriate circumstances, FDA has long used “fewer and smaller” clinical trials as the basis for approval. The reason is that medical research is increasingly discovering biological indicators, or "biomarkers" – such as variants of DNA sequences, the levels of certain enzymes, or the presence or absence of drug receptors – that can dictate how patients should be treated and to predict the likelihood that the intervention will be effective or elicit dangerous side effects.

The presence of biomarkers enables drug companies to better select patient populations for clinical trials to demonstrate efficacy. The reason is related to the statistical power of clinical studies: In any kind of experiment, a fundamental principle is that the greater the number of subjects or iterations, the greater the confidence in the results. Conversely, small studies generally have large uncertainties about results (unless the effect of the intervention is profound) – and that is where biomarkers can make a difference. By better defining the experimental groups – such as limiting the trial only to patients with a certain mutation in their genome or tumor -- they can help drugmakers design clinical studies that will show a high "relative treatment difference" between the drug and whatever it is being compared to (often a placebo, but sometimes another treatment).

As long ago as the mid-1980s, for example (when I was a medical reviewer there), the FDA approved the first genetically engineered human growth hormone product on the basis of a single, very small, pivotal clinical trial. Our knowledge of genetics made that possible. Certain children are from birth unable to synthesize normal amounts of human growth hormone because they possess any of a variety of mutations that direct the synthesis of an abnormal, inactive product, while some completely lack the gene that codes for the hormone. The latter are a special case because if the hormone is administered to them, their immune system recognizes the protein as "foreign" and makes antibodies to it. After a short period of growth, the antibodies bind to and neutralize the hormone, causing the patients to stop growing. In other words, those children won’t benefit from administration of the drug.

For that reason, children who were growth hormone-deficient because they lacked the gene were excluded from the study, and that resulted in a 100% relative treatment difference (that is, efficacy). In other words, every one of the subjects who received the active drug responded, while none of those who got the placebo did. As a result, the FDA was able to approve the drug for marketing based on a pivotal clinical trial with only 28 patients.

Analogous situations are more common now with advances in genetics and the discovery of biomarkers that make clinical trials more efficient. A recently-published study [2] of patients with certain rare pancreatic or gastrointestinal cancers found that by analyzing the “protein-signaling networks” in the tumors, they were able to identify regulators of tumor survival, and they were then able to test the effect of various drugs on these regulators. That enabled them often to predict which drugs would be effective in the tumors – the kind of precision oncology that makes possible smaller clinical trials, analogous to the growth hormone example.
The *Times* editorial went on to criticize the FDA because it “accepts short-term effects (like whether a drug shrinks a tumor) instead of clear clinical outcomes (like whether the drug prolongs life), and ever-smaller improvements in health as sufficient proof that a medication works and is worth selling.”

Those so-called “short-term effects” are also known as “surrogate endpoints.” It’s important to be able to measure the efficacy of new drugs by changes in parameters such as blood pressure (as a surrogate for heart attacks and strokes) and improvement in liver function tests (as surrogates for liver disease). Otherwise, we end up like the two researchers in a favorite cartoon of mine. They are at the lab bench and one of them, who is holding a flask containing a liquid, says to the other, “I think we’ve finally done it: discovered a drug that will confer immortality. The trouble is, it will take forever to test it.” That’s a cartoon that the *Times* should have run.

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[2] https://www.nature.com/articles/s41588-018-0138-4