Expediting Approval

This dilemma, which is a not uncommon one, involves the risks and benefits of expediting approval for a promising drug.

Some years ago, I worked at a pharmaceutical company and was involved in Phase III cancer trials among patients whose disease had returned. These patients had a poor prognosis, but a drug we were working on showed that the median survival rate among the (small group of) patients on the new drug was increased by 5 months. A press release and journal article were prepared and, very rapidly, patient advocacy groups began demanding access to the drug prior to FDA approval.

Once a Phase III trial is completed with results that show sufficient efficacy for FDA approval, it often takes 6 months to 1 year to complete a filing package for the FDA to review, followed by a year before the FDA rules on the drug. So, at a minimum it would take 18 months for approval, meaning that patients who were currently being diagnosed with cancer relapse would probably not be alive when or if the drug appeared. The question therefore was: Could this process be expedited without the loss of data integrity?

While the consequence of routine filing time to desperate patients is obvious, a shortened filing for the pharmaceutical company can mean the loss of data that might be necessary for approval and that could bolster (or diminish) the validity of the efficacy claims. The consequences to the FDA were that taking too long to have the drug approved can look very unsympathetic to the patients who need it, while taking too short a time could potentially put an unsafe drug on the market.

Obviously, both the FDA and the pharmaceutical company have legal obligations to ensure that the drug was reasonably safe and effective. But they also have a moral obligation to provide the medication as rapidly as possible to patients. What kinds of considerations, therefore, need to occur in order to achieve the best of both ethical obligations?

Expert Opinion

Weighing the risks and benefits of a prescription drug is a complex process, made all the more difficult by time and monetary restraints on the process. In an ideal moral universe, the patient with the help of a compassionate, very informed physician, would be able to understand reliable, sufficiently and carefully gathered scientific data and make his or her own decision with a minimum of governmental intrusion. But the real world we live in and take drugs in is quite different.

Pharmaceutical research begins with laboratory investigations, largely funded by the National Institutes of Health (NIH), that seek to identify a biophysiological site or locus for therapeutic intervention. Candidate drugs or biologics are identified and tried. Through complex relationships between the NIH, academic institutions, and industry, the drug is investigated further. A patent on the drug may be issued sometime during this process. Testing in humans usually begins only after a patent is obtained and is, by

law, regulated by the Food and Drug Administration (FDA). Clinical trials, once designed and carried out solely in academic centers, are now often conducted by Contract Research Organizations (CRO's), which are for-profit companies set up to carry out trials for the pharmaceutical industry. The FDA convenes scientific advisory boards to make recommendations, and then decides to approve, disapprove, or require more data on the drug. Expedited approval, with an extra user's fee paid by the drug maker, can be obtained in special situations. The FDA is also responsible for product labeling and warnings.

Once approved, the new drug's maker enjoys a long period of protection from competition—usually 20 years—provided that trials and approval were expeditious and did not eat up a large part of the patent protection time. Post-approval safety oversight is also a mandate of the FDA. Indeed, a case currently before the US Supreme Court (Wyeth v. Levine) is seeking to restrict lawsuits against pharmaceutical companies if the drug has been approved by the FDA.

Informed, ethical people can disagree on whether 18 months or 12 months is the best time limit for FDA approval. But what looms over all this is the fact that persons who are desperate, such as the ones contemplated in this scenario, might very well accept a drug whose evidentiary showing per efficacy and safety is very, very low (e.g., modest evidence from animal models). Needless to say, these individuals would nevertheless be very vulnerable towards the marketing of a drug that might actually have only minimal claim to be taken seriously.

A recent case that demonstrates these concerns is *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*. Abigail Alliance was founded by Frank Burroughs, whose 19 year-old daughter Abigail did not meet inclusion criteria for an oncologic trial. (She later entered a trial for another drug shortly before her death.) What Abigail Alliance would like to see is the current FDA approval process for terminally ill patients largely dissolved or considerably attenuated. Whereas the scenario here contemplates Phase III trials, Abigail Alliance would like to see terminally ill persons be able to access drugs that are in <u>Phase I</u> trials and that "government get out of the way, so that they (i.e., patients) can use their own private resources to fight for their own lives at the inherently uncertain frontiers of modern science." (p. 207 of Jacobson and Parmet)

For Abigail Alliance, the issues are not only beneficence and maleficence, but our country's evolving a largely unregulated pharmaceutical marketplace that can accommodate a certain group of consumers who, calling upon their autonomy and justice rights, wish to make their own purchasing decisions. This would inevitably allow pharmaceutical manufacturers greater opportunity to market unapproved medications.

Abigail Alliance based its legal case on a fundamental right, arguably protected by the privacy and due process clauses of the 5th Amendment. In early 2008, the case was resolved when the US Supreme court declined to hear it, leaving the DC appellate court decision, which said that patients have <u>no right</u> to "a potentially toxic drug with no proven therapeutic benefit" standing. In the meantime, commentators watching the case found a number of things to worry about had Abigail Alliance won.

A very serious worry would be that if terminally ill patients could have access to new but unproven drugs, they would almost certainly not want to enroll in randomized trials but just purchase the drug (because they wouldn't want to chance being randomized into the control arm of the trial). This would not only seriously compromise the possibility and scientific value of clinical trials, but it could profoundly skew outcome data: Patients who are terminally ill and who have exhausted conventional therapies might be too sick for the unproven drug to do any good. Thus, a trial that does not control for participant acuity might show poor results when, in a less sick population, the drug might show better outcomes.

There is also the matter of patients hectoring their physicians for drugs that are not adequately proven. Would this create a liability situation for the physician? What about the pharmaceutical manufacturer? Notice that if Abigail Alliance succeeded in its lawsuit, the pharmaceutical manufacturer might still be wary of making an unproven drug available because of litigation concerns. But on the other hand, the manufacturer might be eager to make the drug available per its perceived profit potential. Thus, an additional concern would be regulating the price the manufacturer charges especially early on, when the opportunity to reap huge profits will be considerable.

As mentioned above, the context of Abigail Alliance was access to Phase I trials, not Phrase III as contemplated by the dilemma contributor. Still, if the concern is about "unproven" pharmaceuticals, then the above worries remain relevant although they are somewhat tempered by a drug's having progressed to Phase III. In that latter regard, it appears we have two ethical issues: 1) selecting an evidentiary threshold for safety and efficacy that is morally reasonable, and 2) recognizing as a matter of justice that the FDA's approval time is possibly prolonged by the institution's being underfunded—an criticism that is commonly made. And while it is true that physicians can always file an application for "compassionate use"—if no comparable treatment alternative exists; clinical trials are underway; and FDA approval is being sought—manufacturers often don't like to accommodate compassionate use requests because they are concerned about litigation and can't profit from it.

Susan Okie has suggested a strategy that seems particularly applicable to the case under consideration: The FDA might allow pharmaceutical companies to sponsor large, nonrandomized, open-access trials for certain drugs. These trials would be run in tandem with traditional, randomized trials such that they would allow greater access while the participants' experiences would be duly recorded in a registry. But because this strategy would reintroduce the fear that patients would flock to these open label trials, criteria should be in place to insure the integrity of the data and promote safety. Such criteria might stipulate that:

1) access to the medications is only available through physicians working in an affiliated oncology trial group;
2) potential enrollees have their diagnostic data reviewed through the physician group and have their staging confirmed;
3) appropriate monitoring of the drug's effects would be recorded by project affiliated labs.

Again, payment and liability issues would have to be decided. Also, conflicts of interest would need to be carefully monitored. Note that the university researcher is under stress to publish positive results and bring in outside money for his own career advancement. The pharmaceutical company has an explicit obligation to maximize profits for its shareholders. Patient advocacy groups are often underwritten by drug companies and so can be conflicted. The taxpayers who fund the FDA want their taxes as low as possible. The politicians who control the FDA's mandate and budget are beholden to their constituencies and the pharmaceutical industries that fund their elections. The insurance companies that pay for the drugs want to limit their price and use. The patient and his physician want the best treatment available as fast as possible.

While the process inevitably calls for a complex balancing of competing ethical principles of beneficence, nonmaleficence, and justice, if the process is tainted, the result will surely be ethically problematic. Conflict of interest policies need to be carefully considered and ethically managed; the FDA needs to have adequate funding to carry out its enormous obligations; government representatives need to be held accountable for ensuring that a transparent, ethical process is in place for drug development, approval, and marketing; and, inevitably, investigators must place the welfare of their participants at the very heart of their ethical obligations.

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