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Editorial

A dual track system to give more-rapid access to new drugs: Applying a systems mindset to the US food and drug administration (FDA)

S U M M A R Y

A widely applicable lesson learned from systems analysis is that a proposed change should always be studied in terms of value to the customer and not a gain in efficiency of any particular component of the system. A systems mindset reveals invalid assumptions that have caused the FDA to substitute its own needs for the needs of its customers (patients). Further, the key constraint to overall system improvement is the lack of consumer choice and competition due to FDA's monopoly over access to drugs. Therefore, we need legislation to implement a proposed dual track system for access to drugs that have successfully passed Phase I safety trials. On one track, an experimental drug would continue with conventional FDA clinical trials. On a new, free-to-choose track, patients, advised by their doctors, would make informed decisions about immediate access to not-yet-approved drugs. Internet access to a government-operated tradeoff evaluation database would provide patients and doctors with up-to-date information on all drug treatment outcomes for both tracks. Dual tracking is a dynamic process that overcomes the limitations of a static FDA regulatory process that ignores individual risk preferences.

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Economists have endorsed the idea of more consumer choices in medical care for some time [1]. But since most people do not think like economists, the idea has gotten little traction with the public. And the FDA, which has absolute control of access to drugs, dismisses the concept of the public having freedom to use not-yet-approved drugs.

Moreover, current FDA policy rests on two assumptions that, in fact, are invalid. FDA says that the use of not-yet-approved drugs outside of clinical trials would: (1) weaken its scientific standard for testing, and (2) impose unacceptable risk on the public. Breaking the hold of FDA's faulty assumptions is the key to improving America's drug-to-patient system (and that includes the research activities that precede drugs entering FDA clinical trials). The systems mindset makes a powerful case for greater freedom in consumer choice.

Lessons from systems analysis

There is a vast literature on systems analysis as well as a body of techniques for performing studies about how systems function. The objective is to develop insights for identifying operational constraints (bottlenecks) in order to rectify them so that system goals can be better achieved [2]. Business firms have been studied carefully as systems because competitors regularly force even successful firms to change or they lose customers to firms providing greater value.

The experiences of business firms offer three important lessons:

- The root cause of the key constraint to improving the entire system's performance can reside in the automatic or unconscious acceptance of invalid assumptions embedded in a widely followed firm policy.

- A tunnel focus on improving local efficiencies often degrades the total system's performance by blocking the overall vision needed to see the key system constraint.
- The performance of a system needs to be judged in terms of the value delivered to the end users of the system, i.e., the firm's customers, and not in terms of the local efficiency of any one component of the system.

Applying these lessons to America's drug-to-patient system would open the way to an improved system capable of delivering more effective drugs, sooner, and at lower cost. Now is an especially opportune time to consider a new approach, in light of the very critical review of FDA capabilities presented in the November 2007 Science Board Report, "FDA Science and Mission at Risk" [3]. Here are just two quotes indicative of the report's overall assessment of FDA:

FDA's inability to keep up with scientific advances means that American lives are at risk. While the world of drug discovery and development has undergone revolutionary change — shifting from cellular to molecular and gene-based approaches — FDA's evaluation methods have remained largely unchanged over the last half century.

...FDA's failure to retain and motivate its workforce puts FDA's mission at risk. Inadequately trained scientists are generally risk-adverse, and tend to give no decision, a slow decision or even worse, the wrong decision on regulatory approval or disapproval.

Insofar as readers find merit in the following analysis, they may be open to the policy option of reducing FDA's monopolistic control over market access to drugs. The last section of this paper describes a dual track system where access to new drugs can be obtained by choosing one of two tracks. On one, patients and their doctors try

to minimize risk by using only approved drugs. On the other, patients, advised by their doctors, can choose not-yet-approved drugs to meet their own personal risk preferences by contracting with drug developers.

The key constraint: regulatory monopoly

The following two tightly knit assumptions are the root cause of the FDA regulatory monopoly being the key system constraint. Both assumptions are invalid and thus acceptance of either renders FDA policy invalid.

FDA rules and procedures should give highest priority to the operation of randomized clinical trials

According to the FDA, randomized, controlled tests (clinical trials) are the “gold standard” for applying the scientific method to evaluate drug efficacy [4]. Who might want to settle for a standard less than “gold”? Perhaps those facing the prospect of a lifetime of chronic pain, disability, or death because approved drugs aren't working for them. Access to experimental drugs via the FDA's compassionate use option, in practice, is permitted only for a very small number of patients. Since FDA has monopolistic control over the drug approval process, no other agency or entity is free to implement any other standard.

As a monopoly that does not itself suffer by ignoring its customers, as do private sector firms who must compete to survive, FDA's testing needs take precedence over customer needs. FDA clinical trial procedures require participants to have certain quantifiable health characteristics so that observed results of the trials might better be attributed to the health condition targeted by the experimental drug rather than to other health variables. But this initial setting of the health-relevant criteria is developed from very limited data and, invariably, only partial understanding of the underlying disease mechanism.

Consequently, there may be wide variation in uncontrolled variables of critical importance to efficacy. But knowledge about the “right” kind of variation reduction is oftentimes discovered only after the trial is completed. Nevertheless, FDA steadfastly defines a successful trial as one that shows benefit based on an average of the entire study population. Strikingly positive results for a retroactively identified subset of the entire population are not permitted to impact the drug approval decision. Rather, they become a reason to design and conduct a new clinical trial. Although true to the science FDA uses to justify its trials, the end result is that the testing process is given a higher priority than the needs of existing patients.

Presumably then, FDA's dedication to clinical trials is for the benefit of future patients. The needs of *existing* patients are valued at close to zero. A case in point is FDA's tenacious opposition to the efforts of the Abigail Alliance to allow late-stage cancer patients access to experimental drugs that have demonstrated, over many years of clinical testing, both safety and efficacy for their intended populations [5].

It is too risky to allow patients and doctors freedom of choice on the use of not-yet-approved drugs

This assumption ignores the fact that people have different preferences for risk versus potential health improvement. Consumer choice allows people to make decisions they believe are in their own best interest. If freedom of choice were allowed, one would expect to observe a range of preferences for late-stage (FDA Phase I safety trial successfully passed) experimental drugs.

That would include zero interest by those who want only FDA fully approved drugs. However, as a person's health changes, their preference could easily change.

If freedom of choice causes a problem for FDA clinical trial enrollments, that is not a reason to eliminate freedom of choice. Rather, clinical testing is one component of a total system. And the solution to a problem should be evaluated in terms of benefit to the end customers. Therefore, the fundamental problem is how best to evolve clinical trial enrollment procedures so that customers benefit.

Because monopolies almost always operate in an environment of inadequate feedback as to system performance, any change at FDA moves at an incredibly slow pace, always clinging to existing policies. A fast pace for medical innovations could result in many new drugs entering the pipeline, only to have them slowly wind their way through Phase II and III clinical trials, even though their efficacy already obsoletes drugs that are FDA approved. It takes on average eight years for an approved drug to have navigated through Phase II and III trials and the FDA's NDA (New Drug Approval) process. Many sick people cannot endure the wait; for example, patients fighting late-stage cancers with life expectancies often measured in months. Many others would choose to not wait that long and, instead, would willingly accept some risk in exchange for access to promising new drugs.

Take the case of the immune-boosting vaccine Provenge to help men with prostate cancer. Years of clinical testing indicated that Provenge was both safe and more effective than existing treatments. During those years of testing, about 30,000 men in the US have annually died from prostate cancer and about 230,000 men are annually diagnosed with this disease. These men and their doctors did not have the opportunity to evaluate up-to-date clinical data for Provenge and then to make an informed decision on whether or not to use it. Despite an Advisory Committee vote of 17-0 that Provenge is safe and a 13-4 vote on efficacy, FDA denied approval. Apparently more clinical testing is what FDA wants. Many men with prostate cancer want Provenge [6]. Is it not possible to have a system that would accommodate both clinical testing and freedom of choice?

The limitations of FDA's regulatory monopoly have become more apparent with the advent of personalized medicine that holds promise for health improvement through attention to genetic differences among individuals. The deficiency in FDA scientific expertise for dealing with personalized medicine, noted in the FDA Science Board Report, will act as a “brake” on innovation. Continuing to demand outdated and expensive clinical tests eliminates drug developers' profit incentive to develop personalized drugs to treat small, targeted groups of patients. Moreover, personalized medicine could even tailor a drug to fit a *single individual*. How would FDA statistical analysis handle a clinical trial population of one? The dual tracking system proposed here-in turbo-charges personalized medicine through freedom of choice.

Tunnel focus

The entire FDA organization is geared to answering, and defending its answer, to this question: Is a particular drug safe and effective? Totally missed is the possibility that their tightly regulated process is a severe constraint on total system performance. Consequently, the fundamental goal gets diverted from overall system performance measured in delivering value to customers and toward that of protecting the testing process itself.

For any system, long-term success in satisfying customers depends critically on continual innovation. For the drug system, the primary challenge is innovation — obtaining breakthrough insights

that increase knowledge of the causal mechanism of a disease. Such insights lead to better hypotheses for formulating new and improved drugs.

As mentioned above, FDA's highly regulated clinical trial process requires a fixed number of patients screened to reduce variation in their health profiles. The primary incentive for drug developers then is to produce only the specific data needed to successfully pass FDA's statistical milestones.

From a total system perspective, drugs should be evaluated in such a way that as safety and efficacy are increasingly demonstrated, the system accommodates an ever-larger number of patients with an ever-wider variety of health and genetic profiles. Ideally, this would be coupled to a rapid availability of data useful to a diverse group of doctors, drug developers and researchers. In contrast, today's clinical trial data is often difficult or impossible to get. Researchers are denied access to information that might well enable them to direct their efforts away from dead ends and toward more potentially useful discoveries [7].

But under the strict FDA policy of preventing "unregulated" drug use (in order not to disturb clinical trials), all the benefits from the use of not-yet-approved drugs as well as the value from related observational data, is cut off from consideration. Although there are challenges in ascertaining direct cause and effect relationships from non-clinical (observational) data, would not drug development firms and research organizations be enthusiastic about obtaining this new data? Except for the FDA, everyone is hurt by the loss of knowledge that could be gained from a large number of voluntary, non-clinical trial users [8].

In an environment of consumer choice, the number of patients who opt to use not-fully-approved drugs would be providing unambiguous feedback to FDA on how much clinical trial testing consumers feel is in their interest. Without this feedback, there is no reliable way to decide whether more or less clinical testing offers net value to the public.

FDA's needs vs. consumer needs

This paper argues for the public to be allowed to choose to use drugs which have completed Phase I safety trials and successfully entered late-stage clinical trials. Obviously, giving more patients access to these drugs could increase health risks for some patients. But it would also reduce risk for other patients who now suffer or die because promising drugs are unavailable until final FDA approval. Why does FDA give so much more weight to the possible increase in risk than to the likely decrease?

It is because FDA's top institutional priority is to avoid the damning publicity that arises when a drug approved as safe and effective shows unexpectedly high adverse side effects, including death. Of course, patients also want to avoid harmful products. So, FDA needs appear, on the surface, to coincide with customer (total system) needs.

Yet, an overly cautious FDA imposes excessively long testing requirements that cause unnecessary suffering and death due to delayed access to drugs [9]. An overly cautious FDA also rejects drugs that could benefit some patients. The opportunity cost is huge, but barely visible to the public. And, to no surprise, the history of FDA is one of steadily increasing clinical testing demands [10]. This story of out-of-balance incentives is well known and often told by economists who point to excessive drug regulation and lack of competition [11].

There are other important economic insights into the differences between FDA needs and customer needs. From an economic perspective, in a marketplace where customers are free-to-choose among different products, competition serves four vital functions:

- Provides direct feedback via product sales of how customers perceive value;
- Segments heterogeneous customer populations, e.g., meeting the needs of people who prefer early access to experimental drugs;
- Continuously squeezes out and eliminates activities that do not add value; and
- Rewards innovation as decided by consumers in the marketplace.

These functions of competition, which occur naturally, have the potential to lead to continuous system-wide improvements [12]. But, FDA insulates itself from competition.

The benefits from competition that increase consumer choice are enormous. Obviously, moving away from FDA's monopolist power and way of doing things would be initially disruptive to the FDA, but even this should be seen as a benefit. The US Postal Service was severely disrupted by the arrival of FedEx, which ended the Postal Service's monopolist power and methods. But that disruption then led to faster innovation, better customer service, and even an improved Postal Service operation due to finally having to face competition.

Everyone wants a better drug-to-patient system to deliver effective health treatments, today, at an affordable cost, and much better health treatments in the future. By implication, this goal calls for (1) boosting cost-effective innovation through scientific breakthroughs and (2) implementing change geared to the total system and the related effect of delivering value to customers – not solely on a localized effect on clinical trial operations. This total system orientation is currently totally ignored.

Solution: dual tracking

Systems analysis has been used to identify the key constraint as FDA policy based on two invalid assumptions. These assumptions need to be abandoned for the system to be meaningfully improved.

The key idea here is that an access to drugs path *around* FDA rather than *through* a reformed FDA must be implemented. Simply put, patients advised by their doctors would take responsibility for deciding if late-stage experimental drugs offer a better opportunity for them compared to FDA-approved drugs. This new path is dual tracking [13].

In contrast to FDA's assumptions, the dual track system is rooted in two different assumptions: (1) *today's* patients ought to be the system's top priority, and (2) the power to make medical decisions rightly belongs, first and foremost, with patients and their doctors.

The basic idea of dual tracking is illustrated in **Exhibit 1**. On one track, an experimental drug continues along traditional FDA clinical trial testing procedures. On a new, separate track, independent of FDA, patients would be able to contract with a drug development firm to buy a not-yet-FDA-approved drug after it has passed its FDA Phase I safety trial.

In the dual track system, patients and their doctors have access to up-to-date information on drug treatment outcomes and all side effects from both tracks – the FDA clinical trial track and the new free-to-choose track. The information would be accessible via the Internet from the tradeoff evaluation database (TED), shown in **Exhibit 2**, which enables patients and doctors to make informed decisions [14].

An important obstacle to overcome is drug developers' fear of being sued by users who experience adverse side effects. Therefore, legislation needs to be passed to specify the information about experimental drugs deemed adequate for patient informed consent. Drug developers, as well as doctors, who follow the prescribed procedures, would be granted immunity from lawsuits

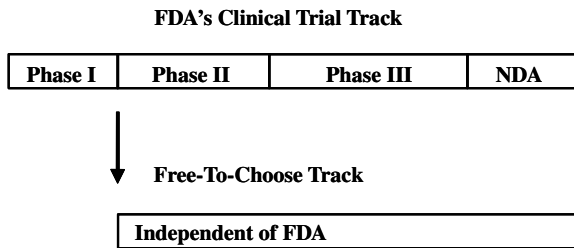


Exhibit 1. Dual tracking.

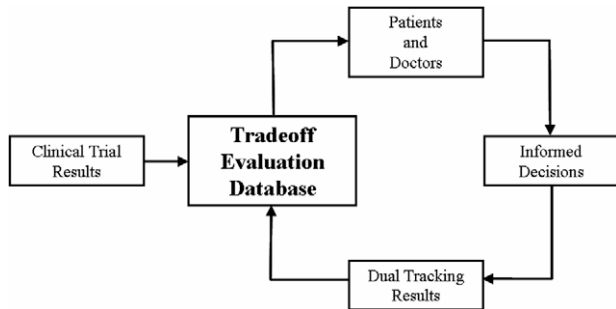


Exhibit 2. Tradeoff evaluation database (TED).

stemming from adverse side effects. That is, patients agree to take the risk of using not-fully-approved drugs in order to have access to them.

As part of dealing with liability, government oversight of the operation of TED is required to ensure adequate, understandable information is available publicly. Since dual tracking is designed as a competitive track to the “as is” FDA process, it is critical that TED be operated independently of FDA.

Benefits

In a dual tracking world, benefits would naturally flow from the arrival of consumer choice and competition. Total system performance would improve as follows:

- Drug treatment outcomes would become common knowledge through TED. Patients and doctors would know what drug developers know. In addition, doctors would be empowered to a far greater extent to improve their patients’ health by being able to use their unique knowledge of their patients and the doctors’ own problem-solving skills in combination with this real-time database of outcomes and effects.
- Information on experimental drugs’ effectiveness, plus relevant patient details would be sent by doctors to TED. Those not-yet-approved drugs that would produce strikingly good (or bad) outcomes would accelerate (decelerate) in usage. This would lead to a large and expanding database on promising new drugs, plus much less expansive, but still valuable research data on poorly performing drugs. This would represent, for all parties, a treasure trove of observational data for generating new and more informed hypotheses. Moreover, individual doctors would learn about the experiences of a larger number of patients than those in clinical trials, including patients with more diverse problems and health profiles relative to clinical trial patients. The “entry price” for the free-to-choose track should be a liability

release and the provision of biomarker and genetic information that would, in turn, serve the greater good through knowledge building.

- The number of dual tracking “risk takers” could vastly exceed the number of patients in clinical trials. This would provide expedited and improved assessments of safety (which require a large number of observations) thereby addressing FDA’s concern about quantifying the risks of adverse side effects. Even with personalized medicine targeting small populations, there is also an ongoing need for diversity among patients. This facilitates generating new hypotheses about cause and effect.
- Private sector information technology firms would likely respond to the business opportunity to access TED and develop specialized information products attuned to the various needs of patients/doctors, drug development firms, research organizations, and possibly even FDA itself. Also note that from analyses of findings reported in TED, positive treatment responses for a drug could be identified for a new subset of patients. The findings could be further evaluated in a timely and efficient fashion with more dual tracking usage by these types of patients.
- The innovation process would accelerate due to better and faster resource allocation. That is, with dual tracking, far earlier recognition that firms have developed a breakthrough new drug would occur. Firms would be motivated to achieve, and benefit from, demonstrated success in treating patients revealed by early sales of not-yet-approved drugs. This impact would be especially pronounced for smaller firms that demonstrate high scientific skill, yet lack the regulatory navigation skills that large firms have in dealing with FDA bureaucracy. The net effect would be more drugs entering clinical trials, faster recognition of the degree of any one drug’s effectiveness, and quicker abandonment of underperforming drugs.

Conclusion

FDA reforms invariably fall into the trap of tunnel focus on one part (e.g., clinical testing) of the drug-to-market system. In contrast, from a systems analysis perspective, the focus is on delivering value to the customer. That also leads to dual tracking. Credible benefits include reduced patient suffering and death, an increase in innovation because of expanded information flows, and lower prescription drug prices, all as the results of freedom of choice, competition, and streamlined clinical trials.

The systems mindset helps one to visualize the new dynamics of dual tracking. That is, patients *voluntarily* participate in a process driven by their choices intended to best meet their preferences for risk and potential health improvement. Patients and doctors, not FDA regulators, decide on the preferred balance of immediate access, wait for more TED information, or only use FDA-approved drugs. Such a dynamic process overcomes the limitations of a static regulatory environment that ignores individual risk preferences.

What would be a productive first step? Let’s start with the FDA’s Accelerated Approval program. Originally intended to expedite the availability of promising drugs for life threatening diseases, this goal was not reached in a broad way due to FDA fears of inadequate testing. If given a voice, patients and doctors dealing with life threatening diseases would prefer a dual track system in place of the Accelerated Approval program. Politicians need to make this happen for their constituents.

The resulting field trial would be extraordinarily helpful in evaluating the experiences of dual tracking patients. Success on a limited scale would justify expanding dual tracking for all new drugs.

Finally, dual tracking rests on a principle that appeals to many Americans of all political affiliations. That compelling principle is: People ought to be free to try to improve or save a life, even if doing so incurs some risk. There is a real urgency to implement this principle now instead of allowing the slow march of FDA clinical trials to continue.

Here is one recent example. Antigenics Inc., a small biotech company, recently completed a very large Phase III trial of its Onco-phage drug to treat kidney cancer. Even though an important subset of patients showed remarkably positive responses, FDA did not approve the drug since FDA clinical trial end points were not met.

FDA recommended that Antigenics do another time consuming and expensive clinical trial on the same identified subset of patients. But, should not patients/doctors have the choice *now* whether to use this drug? Especially those patients who fit into the subset that showed very positive responses? The Russian Ministry of Public Health agrees with the practicality of this and Onco-phage is now approved for patients in Russia. Isn't it ironic that there is greater freedom to choose new medical advances in Russia than in the US?

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Bartley J. Madden
Heartland Institute, Suite 903,
19 South LaSalle St., Chicago,
IL 60603, USA
Tel.: +1 3123774000.
E-mail address: bartmadden@yahoo.com