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WHAT IS THE VALUE OF AN FDA APPROVAL IN A JUDICIAL MATTER?

*Michael A. Friedman, M.D.**

INTRODUCTION

The central role of the Food and Drug Administration (FDA) in our daily lives is so great that no single, brief paper permits a deep or nuanced discussion of any of its many components, much less the legal framework of FDA drug provisions. Consequently, this paper provides a condensed view of a few topics that, from a judicial perspective, might be the issues of greatest interest to a presiding judge.

The range of FDA responsibilities is vast and complex, and includes food, medical devices, veterinary products, blood, vaccines, cosmetics, and over the counter remedies.¹ Here, I will focus only on pharmaceutical products. In the interests of full disclosure, my views are entirely personal (certainly not FDA's) and informed by my own experience. I have participated, one way or another, in almost every aspect of the health care system that might affect a judicial consideration. I have practiced medicine and taught at an academic medical school. I have worked for the federal government, both at the National Institutes of Health and at the Food and Drug Administration (where I served as Acting Commissioner). I have worked for a pharmaceutical manufacturer, and now I am back in academia as President and CEO of the City of Hope. This aggregate experience means, I hope, that my

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¹ See Dep't of Health & Human Serv., U.S. Food & Drug Admin., Products FDA Regulates, at <http://www.fda.gov/default.htm> (last visited Mar. 7, 2004).

remarks will neither be perceived as too defensive of any one of these institutions, or totally uninformed. But, there is always the danger of a subtle, unintended bias.

Were I sitting on the bench and judging a case involving a drug product, there are two questions I might consider with reference to the FDA approval process. They would be: (1) is the regulatory process a rigorous one and, (2) are the regulatory findings accurate. These two concerns necessarily go hand in hand in determining the evidentiary value of an FDA drug approval.

This paper consists of three parts: first, a very brief description of the general process of pharmaceutical product development (R&D), which provides relevant background about how research information is generated by a pharmaceutical manufacturer and presented to the FDA for review; second, an equally brief description of the FDA review process; and third, an examination of some of the characteristics and limitations of this review FDA process.

I. PHARMACEUTICAL R&D

A. *The Process*

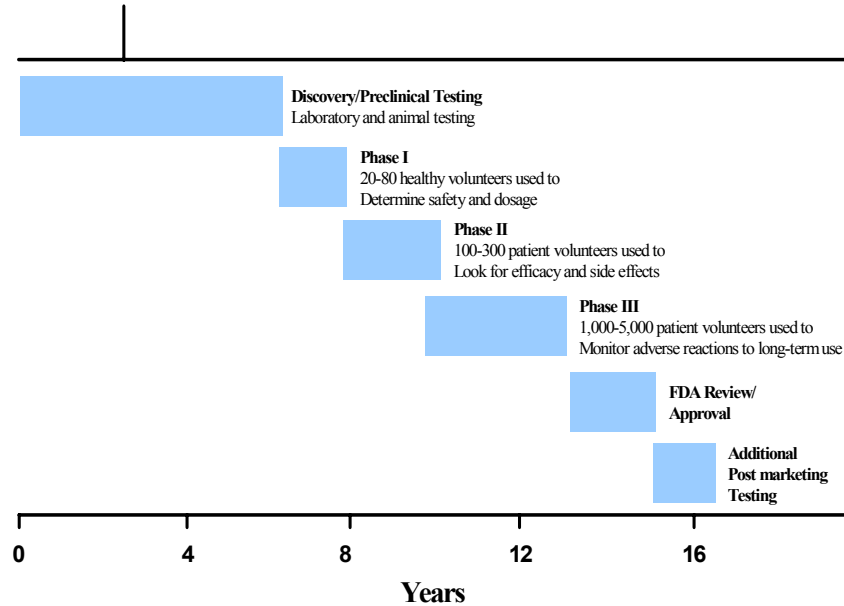
The complex difficulties of developing a new drug product are truly formidable. Figure 1 is a schematic that generally represents a process that often takes more than 15 years.² A substantial component, perhaps one third, of this expensive and complex process is the screening of molecules, in vitro testing, and animal studies to try and identify a suitable biological target and find molecules that affect that target in some clinically useful way.

² See FDA CTR. FOR DRUG EVALUATION & RESEARCH, FROM TEST TUBE TO PATIENT: IMPROVING HEALTH THROUGH HUMAN DRUGS (3d ed. 1999), available at <http://www.fda.gov/cder/about/whatwedo/testtube-full.pdf>; see also Richard J. Findlay, *Originator Drug Development*, 54 FOOD DRUG L.J. 227, 227-28 (1999) (stating that the development process for a new drug takes an average of 14.7 years).

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FIGURE 1—TYPICAL DRUG DEVELOPMENT TIME



Next, clinical testing in humans can begin. First, initial toxicity and pharmacology studies (Phase I) are conducted, followed by preliminary efficacy trials (Phase II), and then, large randomized studies are used to definitely identify the benefits and get more precise information about the toxicities of that particular medicine (Phase III).

There are interactions between the industrial sponsor and FDA throughout this entire sequence. At the end of this process, there is FDA review and, if appropriate, approval for commercial marketing. Thereafter, for almost every product there continues to be additional post-marketing studies. The post-marketing studies (Phase IV) are among the most important of all, because even after a 15-year, \$900 million effort, at the time of FDA approval there is relatively limited prescribing information available. Simply put, we learn progressively much more information about a product over time.

As an investor, from a purely financial point of view, it would probably be more prudent to invest in oil prospecting than in

pharmaceutical development. With modern geology techniques, wildcatting for oil wells is statistically more successful than finding a new drug that goes to market. Perhaps only one in 5,000 screened candidate molecules even begins development. Only one fifth of those actually complete clinical trials. Only one third of those are finally completely approved by FDA. So, overall, the odds of success for a new drug are not at all favorable.³ This represents, if you will, a winnowing process through which all products need to pass.

The costs of completing all these steps are enormous. In 1976, the average cost of developing a new drug was about \$167 million. Today, it is in excess of \$900 million.⁴ This figure does not mean drug development is necessarily being well done nor that the data derived from R&D studies are necessarily more valid, useful, or appropriate. This is simply the conventional cost of performing this kind of research to bring a product to market, and there are many reasons why drug discovery and development are so very difficult.

B. Why Is Drug Discovery So Difficult?

The basic hurdle is that new drugs are, by their nature, new. The targets are new; the toxicities will be new; the nuances of how to use the product will be new.

Second, no matter how carefully we screen compounds in animal model systems, the differences between mammalian species are dramatic, vast, and incompletely understood. So, although we may derive a lot of useful information from mouse, rat, and dog studies, we do not have all the relevant information necessary for human use.

Third, people vary and so do diseases. Even when we focus on a particular disease category (like diabetes or cancer) we realize

³ Henry Grabowski, *Pharmaceuticals: Politics, Policy and Availability: Patents and New Product Development in the Pharmaceutical and Biotechnology Industries*, 8 GEO. PUB. POL'Y REV. 7, 8-10 (2003).

⁴ See FDA CTR. FOR DRUG EVALUATION & RESEARCH, *supra* note 2, at 15 (stating that a company like Hoffman-La Roche spends about \$1 billion in research worldwide). Parenthetically, while some in the pharmaceutical industry are proud of this fact (\$900 million cost), I think it is appalling.

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that there are many subtypes and forms. Moreover, nature tends to be rather conservative. Just when you think you have found a way of exploiting a biologic opportunity, you find that it is too toxic or not medically successful. Another way of saying this is, you do not get something for nothing in pharmaceuticals (or in medical interventions of any sort). Science, notwithstanding what scientists sometimes proclaim, is incremental and incomplete. For every biologic question that is answered, a dozen more are raised that are more vexing and more formidable. There certainly are no shortcuts.

Furthermore, there are some very fine pharmaceutical companies and very competent scientists who spend their entire careers trying to develop better drugs. Yet, I think it is safe to say that in this endeavor no one is truly an expert; no one has a full understanding of the development process. It is getting more and more difficult to develop new drugs and the business and scientific decisions are very tough and the risks are very high.

II. FDA REVIEW

FDA review begins prior to the first human administration, and, in a sense, never ceases. Even after a drug is approved for sale, information is still gathered on that drug, albeit less intensively, less formally, and less regularly. Nonetheless, it is still gathered. Although the approval of a new product is a sort of watershed, it is not the final point in understanding how to optimally use that medication or what its side effects may be.

There are formal meetings that take place between FDA, the drug sponsor, and the pharmaceutical company, all at specified time points, usually before the initiation of major clinical trials. Additionally, there are informal meetings that may occur any time—telephone meetings, face-to-face meetings, and exchange of written materials and so forth.

All of the animal data, the toxicology, and the pharmacology data are reviewed, and then all of the clinical data are reviewed. In fact, there is a scrutiny of the primary data. What does this mean? There are often several thousand patients in the clinical dossier that a company presents to the FDA. And, in fact, over the past two

decades the size of that dossier has grown. Today, it is typical to have 1,000 to 5,000 subjects. For some products as many as 40,000-50,000 patients/subjects may be studied. While 50,000 may seem like a large number, it is actually only minimally satisfactory.

All the primary clinical information about the subjects—pathology reports, x-rays, blood reports, etc.—is made available for FDA review. Typically, FDA does not review every single case record individually. In a study where there may be dramatic benefit, however it would not be unusual to have FDA review those materials that document the purported efficacy (and to do so in some considerable detail). There are also on-site inspections. If there are 100 hospitals that participate in a clinical trial, FDA may visit some of those hospitals, go to the radiology department to look at pertinent x-rays, or go to the medical record room to review patient files to make sure that the data reported in summary form is actually supported by the primary documentation.⁵

Formally noted review interactions occur when FDA meets with the sponsor. These are summarized and memorialized. When the entire body of information is finally prepared for a definitive regulatory decision, there is often (but not always) a public advisory committee meeting. A group of scientists and lay representatives who do not have any overt conflicts of interest analyze the dossier materials at a public hearing. The pharmaceutical manufacturer makes a presentation, the agency makes a presentation, there is time for comments from the audience (from patient advocacy groups or individuals), and there is an open discussion of the value and the toxicity of that product.

The United States FDA also communicates with sister foreign regulatory bodies, such as the European Union Food and Drug Administration and the Health Protection Agency of Canada, to distribute information shared and perspectives.

⁵ See U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, *at* <http://www.fda.gov/cder/about/smallbiz/humans.htm> (last visited Mar. 7, 2004) (describing Institutional Review Board's procedures on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research).

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III. FEATURES OF FDA REVIEW

What are the characteristics of FDA review? Briefly, the overall review process is a good and thoughtful one with a number of strengths and advantages. First, there is no consistent or systematic bias. This is a scientifically sophisticated, objective review of information. The potential for conflicts of interests are minimized. Every agency official or reviewer has personal, social, economic, intellectual, philosophic, and even political perspectives. These are certainly recognized, but their impact is minimized within the agency. FDA staff overtly act in a way to give the best, dispassionate review of information. Moreover, there are multiple layers of expert review so that a junior reviewer has her review scrutinized at the next administrative level and so forth. Some very important product decisions are elevated, even to the level of the commissioner, to assure that there is a critical re-evaluation of all of the judgments and processes that have gone into formulating that decision. To its advantage, this process is moderately transparent. Except for patented intellectual property and certain commercial confidential information, everything else is disclosed to the public.⁶

So, the clinical information, the patient summaries that are used to determine survival or toxicity or efficacy information, are made available to the public for their scrutiny and evaluation. It should be recognized that although the statutory basis for review (the Food, Drug & Cosmetic Act, for example), directs that a product be “safe and effective” in order to receive FDA approval, this is really a relative standard, not an absolute one.⁷ As everyone appreciates, nothing, and certainly no medication, is entirely “safe.” It is well documented that an 81mg “baby” aspirin can rarely cause a fatal stroke or a massive stomach hemorrhage. A

⁶ See U.S. Food & Drug Admin., Ctr. for Drug Evaluation & Research, Institutional Review Boards and Protection of Human Subjects in Clinical Trials, at <http://www.fda.gov/cder/> (last visited Mar. 7, 2004).

⁷ 21 C.F.R. § 314.105 (c) (1999); Jill Wechsler, *Risk Management Shapes FDA Policies and Practices; Washington Report; Controls to Ensure Safety of New Drugs*, PHARMACEUTICAL TECH. Aug. 1, 2002, at 12 (stating that no drug is 100% safe).

product that is given to millions of people every day can (in rare instances), unfortunately, be lethal to a particular individual. Similarly, nothing is universally efficacious. No matter how good a product is, no matter how “effective” it may be for the majority of patients, no product helps every single patient. And so we have to recognize that the legal standards here are not ideal—rather, in the real world, they are relative.

While FDA’s most comprehensive and most critical reviews are the careful assessments made at the time of initial product approval, this may not be the only important review. There is routine monitoring of accumulated data after a product is made commercially available.⁸ But this capture of post-marketing information tends to be relatively inconsistent. Consequently, only infrequently does formal FDA re-review have the same characteristics as the primary review and approval. The initial review is a powerful means for detecting large biologic signals. Dramatic benefit or unusual or frequent side effects can be easily recognized. However, this initial review is less effective for detecting subtle (but important) signals. This should not be construed as a criticism of the FDA reviewers or the process as it exists. It is just that for very subtle toxicity, or side effects that are inconsistently or unpredictably observed, or toxicities commonly attributed to other factors, the initial review may have limited utility.

One source of confusion is with the evaluation of common or mild toxicities. A brand new product may cause headache. But, headache is a rather common complaint (one that people experience all the time). It is difficult to distinguish between a headache that is a side effect of a drug and a headache that we all suffer (for any number of reasons). The ability to detect rare, but critically meaningful adverse events may not be simple; thus there are clear limitations of the regulatory approval process. For example, the number of patients included a typical dossier that is submitted by a drug company for FDA review today will almost certainly grow in size over the next decade. With a clinical sample

⁸ Lara Noah, *Informed Consent and the Elusive Dichotomy between Standard and Experimental Therapy*, 28 AM. J.L. & MED. 361, 394-400 (2002).

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denominator of 10,000, you can reliably detect an important, novel toxicity (one typically identified in the average package insert) at about the 1% level. However, you might need 750,000 subjects to even be able to accurately perceive a rare (but lethally important) toxicity and recognize that it is a real signal (and not just confounding background noise).

In practice, drug recalls and civil actions are based upon critical side effects occurring in only 1 in 250,000 to 1 in 500,000. So, a drug like Duract, a non-steroidal anti-inflammatory drug that caused fatal liver toxicity extremely rarely, was not clearly perceived to be a risk until some 2.5 million people had taken it.⁹ While the number of people who suffered serious liver toxicity was extremely small, the drug was removed from the market because it is unacceptable to have even this tiny chance of liver toxicity when there are inexpensive, safer, and easily available alternatives (such as ibuprofen).

In order to reliably detect a rare but important toxicity, however, you may need many millions of individuals exposed, although it is inconceivable that you will have millions of individuals evaluated as part of the primary review. Were that the case, almost no new drug would ever be approved. So, no matter how good the initial screen is, it will only be later, when the drug is in widespread distribution and broad use, that you are able to detect some of the most critical and important side effects.

If, as I maintain, that FDA review is rigorous but imperfect, there are several sources of “error” that need consideration. By “error,” I mean conclusions, which at a point in time appear to be valid, but which actually are not (that is, they are different from reality). The most infamous, but actually the rarest cause of error, is outright fabrication—the determination that the submitted dossier is purposefully false. For example, this might happen if the investigator did not do the experiment or faked patient data. Such occurrences are very dramatic and they are usually well publicized.¹⁰ By every measure they seem to be exceedingly

⁹ Barbara A. Noah & David B. Brushwood, *Adverse Drug Reactions in Elderly Patients: Alternative Approaches to Postmarket Surveillance*, 33 J. HEALTH L. 383, n. 7 (2000).

¹⁰ See FDA CTR. FOR DRUG EVALUATION & RESEARCH, *supra* note 2, at

uncommon, but they certainly do occur.

Such falsifications are detected by scientific replication. For instance, if a manufacturer fraudulently claims that it “has a treatment that cures AIDS patients,” that medicine is thus approved, and then lots of other physicians prescribe that marketed medication and it does not cure AIDS patients, scientific journals will begin to publish studies that say the medicine does not in fact work. The product will be recalled or reexamined because scientific replication will eventually show that there has been a major lie.

More commonly, but still relatively uncommon, is sloppiness. The distinction between purposeful and accidental error from a patient point of view is null. By this I mean that although the one is evil and the other is just clumsy, they are both utterly unacceptable. Misinformation, no matter how innocently generated, still does harm. But how do you guard against sloppiness? It is by that elaborate system of reviewing primary patient records, comparing data tapes and files to the original materials, and making sure that data entries are accurately transcribed—issues as simple as making sure that you do not mix up records from Patient A with Patient B, or Study 1 with Study 2.

One difference between these types of “errors” is that sloppiness is not systematic. It results in results that are as often positive as negative. If an investigator is simply mischaracterizing information, he might record that the patient got better when, in fact, the patient got worse. However, it is just as likely to say the patient got worse when the patient actually got better.

Again, this “error” is detected by scientific replication, and it is not a commonly encountered problem. What is a much more common and serious confounding variable is biologic heterogeneity.¹¹ In fact, it is universal. By this I simply mean that everyone is different. This is obvious, but it is an underappreciated fact. With respect to age and gender, race and comorbid conditions people vary greatly. Some people have

24-25 (discussing fabrication of some medical experiments in which the patients were unknowingly subjected to certain drugs).

¹¹ See U.S. Food & Drug Admin., *supra* note 6.

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hypertension; some have diabetes; some have asthma. Some people have several kinds of diseases simultaneously. How do those co-morbid conditions influence an interpretation of the risks or benefits of a medicine? Someone may be taking an antihistamine and also may have a history of migraine headaches. Everyone has different medical conditions and has a different constellation of physical attributes and findings. Likewise, not only must one consider concurrent prescription medications, one must also consider dietary supplements, or vitamins, or other over-the-counter medications.

Finally, there is the overwhelming condition of humanness—our mosaic genetic uniqueness. It is what makes people wonderfully varied and also makes it so terribly difficult to develop new drugs. Since everybody is biologically different, trying to characterize how a product will affect a whole population of people is going to necessarily be imperfect and imprecise.

What are some of the explanations for lack of efficacy or severe toxicity? These are questions encountered every day by judges on the bench. Someone says, “I didn’t get the benefit that was promised.” Or, “I got a toxicity that I didn’t anticipate or I wasn’t warned about.” There are a large number of possible reasons, but commonly encountered ones include the following: First of all, the patient may have had the “wrong” condition. There may have been a misdiagnosis. Perhaps the physician thought that the patient had diabetes, when actually the patient had a rare form of adrenal tumor. Both conditions can result in elevated blood sugar but there was a misdiagnosis. The patient was treated with a medicine appropriate for diabetes, but the patient actually had a different disease. Perhaps the patient actually had diabetes, but the doctor mistakenly prescribed a medication that he thought was for diabetes. Perhaps this particular medicine really is not effective for diabetes patients—he made a mistake. Or there was simple confusion—the name of two medicines sound similar, or the pharmacy dispensed the wrong drug, or the physician was sleep deprived that day, or whatever other excuse.

Alternatively, the medication prescribed was completely appropriate for that condition, but it was prescribed at the wrong dose or schedule. Instead of taking it for two weeks, the patient

took it for one day. Or the patient took it every other day. Or the patient stopped taking the medication before they were supposed to. Was that because of physician error? Did the physician write, "Take this every day for two weeks and do not stop." Or, "Take this indefinitely?" Or was there patient error? The patient may say, "You know, I just do not like to take drugs. I know that doctor gave me the medicine, but I am not going to take it." Or, "I am not going to take it three times a day. I will take it once a day. And maybe I won't take it for two weeks. I will take it for two days."

There is also recognized heightened sensitivity to toxicity for certain patients with certain disease or metabolism variants.¹² We know that in every drug package insert there is information on how many patients are likely to have a toxicity (such as a skin reaction). Although there is general information, we are usually unable to accurately predict which particular patient will have which serious side effect.

Moreover, we may be able to describe side effects, but there may be disagreements about what constitutes a major "side effect." It is like definition of major surgery (popularly attributed to Mel Brooks). That is, "minor surgery is anything that happens to someone else, but major surgery is any procedure that I have." Moreover, for patients who are critically ill and have few if any alternatives, the tolerance for more toxicity is greater.¹³

Finally, (sadly) there are a host of unknown factors that physicians and scientists poorly understand which determine efficacy and toxicity. In this regard, the importance of accurate adverse event reporting cannot be exaggerated. Unfortunately, however, these events are only infrequently reported. It is even difficult to ascertain what fractions are properly captured. It is popularly believed that less than 10% of the true adverse events are reported. Even when they are reported, they may not be reported

¹² See U.S. Food & Drug Admin, *supra* note 6 (discussing elderly people's heightened sensitivity to due to drug metabolism and interaction problems).

¹³ See Vivian I. Orlando, Note and Comment, *The FDA's Accelerated Approval Process: Does the Pharmaceutical Industry Have Adequate Incentives for Self-Regulation?*, 25 AM. J.L. & MED. 543 (describing how terminally-ill patients advocated for accelerated approval of new drugs by the FDA, even though information about the drug's safety and effectiveness was preliminary).

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accurately.

Adverse Event Reports are toxicities that are unusual, or unanticipated, or severe, and come from a variety of sources.¹⁴ They are reported to FDA sometimes by the health care provider. The manufacturer is charged with gathering this information and regularly sending it to FDA. At FDA these data are tabulated and analyzed. With sufficiently clear information there are good examples where the agency has taken definitive action.

CONCLUSION

Since we all learn a lot more about a drug after more patients take it over longer periods of time, FDA must watch carefully and be prepared to act. So what then is my estimate of the meaning, the value, of FDA review? I deeply respect the agency and the scientists and staff who work there. It is like many large bureaucracies. There are, of course, some less motivated and less talented staff, but generally it is an agency made up of incredibly well-intentioned, hard-working, smart, principled individuals. Very strong general information is provided for populations of patients who are subjects. Information that is reliably valid. I think there is useful information provided about individual patients or subjects, but that information is imperfect (for the reasons that I have outlined above). In some ways it is a problem of epistemology. We know what we know about an individual drug because it is revealed by progressive revelation more often than through a particular epiphany. The FDA review has real integrity and is incredibly important, powerful, and useful. But, by itself, it may not be determinative for a judge sitting on a case. That said, without a doubt, FDA review should help form a substantial part of the basis for a decision.

¹⁴ 21 C.F.R. § 314.80 (1999).