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FDA Policyon Pharmacogenomic Data in Drug Development

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My presentation will address policy and developing public policy in the area of pharmacogenomics. To a great extent, this discussion so far has remained within the drug and device industrial community, the scientific community, and the FDA. I appreciate this opportunity to reach a wider audience.

How is any new science or new technology integrated into existing regulatory, legal, and policy frameworks? We ask these questions in the context of clinical medicine, insurability, and payment, and we ask them each time a new science or technology emerges.

This discussion centers on the new science of phramacogenomics and how it will be integrated into drug development and clinical medicine. First, it is important to understand why pharmacogenomics matters and has to be integrated into drug regulation. The major barrier to having really effective drugs is the variability in the way people respond to drugs and the inability to predict how they are going to respond. These factors drive the cost of developing drugs and cause many adverse reactions to them.

There are two kinds of variability that must be considered. One is variable effectiveness of drugs. Leaving aside antibiotics and drugs that are actually not directed at people—those are actually directed at organisms that get into people—often the measurable effect seen in randomized trials in populations is small. Therefore, sponsors have to conduct large studies of effectiveness. Often, erroneous conclusions are drawn that a drug does not work or that its efficacy is insignificant because the response rate in the population is small. The response may be variable in fact, and some people may respond very well—though the collective response across the entire population studied may appear unimpressive. Unfortunately, at the present time, it is difficult to predict which patients will be responders.

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This same is true on the other side—the toxicity side. All of today's drugs have some associated risks; if you look at a drug tested against a placebo, you see that every drug has a consistent pattern of side-effects over and above what the people on placebo experience. In fact, given enough data, you can identify consistent patterns of both common and rare side-effects. Now, some of these side-effects actually are due to the pharmacologic action of the drug, and there is no easy way to get around that because it is related to the beneficial effect of the drug. So, for example, certain drugs that you take for asthma are going to make you jittery. That is the same physiological effect that is opening up your airways. But a lot of the side effects are medically termed *idiosyncratic*. What *idiosyncratic* means in this context is: We do not know the cause, but there was a cause. We just do not know anything about it, so it is idiosyncratic. The way we approach drug toxicity in development is to expose many people to the drug and catalogue what we see versus placebo; it is all very observational. We say: This is liver toxicity, or this is a kind of organ toxicity, without understanding the mechanistic cause. So, ultimately, we may decide that people with preexisting liver disease should not take a drug because it has liver toxicity while, in fact, those two things may be completely unrelated.

Pharmacogenomics, is the science of correlating drug responses to genetic data—meaning the generation of gene or gene expression data that correlate genes and observed drug responses. Pharmacogenomics with a focus on gene sequences and data is pharmacogenetics.[1] There are many different kinds of data about pharmacogenetics or genomics that correlate with drug responses.

One is simple polymorphisms in genes—for example, single changes in genes that impact the production of enzymes that metabolize drugs in your body. In some cases, if a group of people is given a drug, some will have the *normal* level of the drug in the blood, others have no observable presence of the drug in the blood, while others have a very high level. Of course, polymorphisms are relevant to dosing. Individuals without detectable blood levels will not have any drug effectiveness. Those with extremely high levels from a normal dose often will be dangerously exposed to toxicity. So, simply by knowing the relevant polymorphisms, one can predict the drug exposure that people have. Unfortunately, we do not have easy ways to test for those drug metabolizing genes at the moment.

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1. *Pharmaco* refers to drug or medicine; *genomics* refers to genes. *Genetics* refers to gene sequences.

There are also gene expression patterns. If you take a drug, your genes will start expressing different RNA in response to getting that drug. We know that, if it is a liver toxic drug, your liver will start making little toxic RNA response messages. If one were to look at those liver cells, one could actually say, "Look, that liver cell is experiencing some stress or toxicity." So we could predict, sometimes, toxicity based on gene expression. Another big problem in therapeutics, contributing to the variability of therapeutic response, is the fact that diseases are lumped together for treatment purposes.

At this time, medical practice is predicated on observation. For example, we still collectively categorize *lung cancer* as we did one hundred years ago. We still are not sophisticated. We don't know what the actual molecular cause of that particular cancer is in that particular person because we don't look for it. Gene expression patterns are giving us this opportunity, and there are some breast cancer therapies actually targeted toward whether or not one is expressing certain genes. We also perhaps could monitor and guide therapy based on observed gene expression patterns. Again, we may determine that a patient's liver is looking a little toxic and, therefore, we ought to back off a particular therapy and monitor for toxic responses.

So, in summary, this new science of pharmacogenomics holds the potential to help us better predict effectiveness and avoid toxicity. Pharmacogenomics is being applied extensively in drug development right now to pick candidates products to move into clinical testing. This science has the potential to revolutionize the process and really help people by individualizing therapy. Patients do not want to know if a particular drug is the best one for people with their ailment, they want to know, "Is this the best drug for me?" Right now, we seldom can answer that question with genetic precision; drug selection generally is based on the mean responses of the disease population as measured. Pharmacogenomics could revolutionize both drug development and treatment. Imagine the possibilities for narrowing down treatment to populations most likely to benefit and eliminating populations likely to suffer adverse events.

The primary policy problem right now is that most of these genetic tests are not being evaluated in clinical studies, and they are not being seen by the regulatory agencies. Application in the official drug development regulatory process is stymied by concern about how these tests will be used by the marketing application reviewers. This could present a real lost opportunity for any person who wants to take medicine in the foreseeable future.

So, we need to adopt a regulatory approach that will enable the free exchange of this information. From a public policy standpoint, the goal is to advance the science and to move it along as quickly as possible in a responsible manner because it has such promise to advance therapeutics and to improve human health. There is a real human need that compels the timely development of appropriate regulatory policies—policies for banking data, patenting, and the list goes on. We *need* appropriate legal and regulatory policies put in place to allow things to move forward responsibly. Moreover, we have to integrate our existing—and this is what is often very challenging—regulatory and legal framework with this new science. As a new science emerges, the laws and policies crafted in an earlier time for an earlier type of information, data, or science often become awkward entanglements.

What have we done at the FDA? We have been confronted with this problem for some time, and the field of science we are talking about today is really taking off. Initially, in 2002, we had a scientific meeting between regulators and representatives from the industrial world—the big pharma companies, the bio companies, and the device companies.[2] We invited some academics to talk about the scientific basics, and we exchanged views and tried to identify what the problems and opportunities were. The FDA went back and considered these issues. Then, in 2003, we made a presentation to the FDA Science Board.[3] We proposed developing a pathway for this type of product, a pathway that we would put out for public comment. In November of 2003, we released this proposed pathway, which is a draft FDA guidance document, for public discussion and comment.[4] This is the standard administrative process: We release proposals, open a docket, and receive comments, and then we finalize the document.

Subsequent to releasing the document, we had a large meeting—some 500 people attended this meeting from all different sectors, to discuss the draft proposals and to generate initial comments.[5] Participants included a wide variety of people and

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2. Food and Drug Administration (FDA), Guidance for Industry, Pharmacogenomic Data Submissions 3 (2005), *available at* http://www.fda.gov/cber/gdlns/pharmdtasub.pdf.

3. *Id.*

4. FDA, Draft Guidance for Industry, Pharmacogenomic Data Submissions (2003), *available at* http://www.fda.gov/cder/guidance/5900dft.pdf.

5. The Drug Information Association (DIA), FDA, the Pharmacogenomics Working Group (PWG), PhRMA, and BIO co-sponsored this meeting, which was held on Nov. 13 and 14, 2003.

organizations with interests in drug development. The guidance document comment period has just closed, and we are trying to start on the final version of the guidance.[6] However, I would say, guidances are always open for comment. If anyone here is moved to comment, we will be very happy to get your comment. The document and information about how to contribute to the docket are posted on the FDA's web site.[7]

Now, what did we put in the proposal? Well, the reason there was reluctance to do pharmacogenomic testing in drug development is the following: Sponsors who submit investigational programs to the FDA, which are called investigational new drug applications (INDs) or new drug applications (NDAs) or biologics license applications (BLAs), are required under the law and regulations to provide certain information to the FDA.[8] So, if they generate that information, they must send it to the FDA. These sponsors expressed concern that they do not know how this new information fits into this framework and what the FDA will do with the information. Drug development is already a long, arduous, expensive and very uncertain process, and sponsors expressed reluctance to add any additional uncertainty to the process. That is the bottom line. In addition, the regulations that the FDA operates under were written well before the advent of pharmacogenomics, and so their applicability is unclear. The FDA draft guidance attempts to explain how the FDA's current thinking on this new type of data fits into the current regulatory scheme. We have had to *trim off a few edges* to fit it into the regulatory scheme, but I think we have done a reasonable job.

However we deal with pharmacogenomic (PG) data, submissions must conform with our regulations. Changing regulations is an arduous, time-consuming, and very uncertain process. So, we had to write a guidance that would fit this new kind of data into existing regulations. Much PG data currently available is not well enough established scientifically to be suitable for regulatory decision-making. There are a lot of genotype-phenotype associations out there. There is a lot of hope and linking, and there are a lot of papers on different links, but the scientific and medical meaning is not clear. Given the emerging,

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6. The draft guidance was subsequently finalized in March 2005, and all future references will be to the final version.

7. FDA Dockets Management, http://www.fda.gov/ohrms/dockets/default .htm (last visited Nov. 2, 2005).

8. 21 C.F.R. §§ 312, 314, & 601 (2005).

explosive, and varied nature of this science, we recognized the need for threshold definitions. We started out with the definition that is in the literature for a *biological marker* (biomarker): "A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[9] For *valid biomarker*, we added: A biomarker that is measured in an analytical test system with well-established performance characteristics.[10] This definition reflects that we at the FDA are not going to be able to take data from an unstable or poorly understood analytical system and make regulatory decisions. Once a test itself has good analytical characteristics, there needs to be an established framework or body of evidence, clinical or otherwise, which elucidates the significance of the test results. However, this definition does not fully describe the situation in drug development, which is a dynamic situation where information is evolving and some data may be proprietary. Therefore, we added additional definitions. A known *"valid biomarker,"* is one that is known and accepted by the biomedical community.[11] A *"probable valid biomarker"* is one that has been developed to an appropriate stage by a specific company, but is not widely accepted.[12] This reflects the evolving nature of the information.

How do these definitions impact applications? Sponsors must separate the kinds of data they are submitting and filing with their applications and fit that into categories. For example, they have to distinguish data that are not yet validated, or are not sufficiently understood and are not squarely within the scope of the regulations. The hope is that this will free companies up to do the exploratory pharmacogenomic work that we would like to see them undertake and, consequently, derive discovery of individualized therapies through patient-tailored research. More importantly, we hope to raise the likelihood that the FDA will see more information especially pertinent to safety and effectiveness of drugs.

The FDA has also developed algorithms that require companies to submit data during the investigational (IND) stage if the test results will be used in decision-making in an animal or clinical

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9. Biomarkers Definitions Working Group, *Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework*, 69 Clinical Pharmacology & Therapeutics 89, 91 (2001).

10. FDA, *Guidance, supra* note 2, at 17.

11. *Id.*

12. *Id.*

trial.[13]   The rationale is that such data are an integral part of the trial. If the sponsor is going to say, "We are only going to enroll people who have this genetic test result," then the sponsor has to explain the test and submit the test. We also expressly recognized that it is up to the sponsor to decide whether to use test results in an IND to support scientific contentions about a drug. We also require submission of test results involving a known, valid biomarker. Where there is agreement in the biomedical community, the clinical community or the toxicology community, and this information has known meaning, then it needs to be submitted to the FDA, just as any other safety or effectiveness data have to be submitted to the FDA under the regulations.

People are still worried that this guidance does not solve all the problems, but we think we are at least making progress toward devising a scheme that will welcome the new science into drug development in a responsible manner. Our position also reflects the fact that we would like those inside the FDA to know what is going on—to learn what is happening in this field as it happens so that we can craft reasonable policies in conjunction and be ready to evaluate the data submitted to us. Considerable data generated in drug development programs are proprietary and kept confidential. Gaps in information add a dimension of complication to understanding statistical and analytic problems, with evaluating these data and making sense of them. To encourage voluntary submissions, we have established a voluntary submission pathway, the Voluntary Genomic Data Submission (VGDS)[14] and assembled an interdisciplinary team to manage it.

The VGDS, often referred to as a *research exemption* or *safe harbor provision*, is a mechanism by which companies submit their data and tell us about their exploratory pharmacogenomic work during drug development. Some early adopters have come in and have been eager to show us what they are doing, and we have the opportunity to learn with them. Participants are building FDA knowledge and helping us craft a reasonable regulatory structure without being dependent upon decision-making about a particular drug.

A major question is how will the FDA use voluntary data? There are people who are worried that the FDA will use the data against a submitting company, while others are worried that we will respect the voluntary nature of the submission and confidentiality to the point of not disclosing data that are in our

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13. *Id.* at 5.
14. *Id.* at 7.

possession and are really important. The *valid biomarker* criteria should, however, limit this area of controversy considerably—at least for a while. Unfortunately, for a wide variety of reasons, including the lack of public availability of assays, we are not likely to see valid biomarkers soon except in the drug metabolism area.

A major reason we have the FDA looking across all these studies and developing this guidance is that we need to evolve how the data could and should be handled. When we publish the final guidance, we anticipate establishing an advisory committee and using a public process to facilitate discussion.

Submissions of voluntary data are made under an IND or NDA, which protects confidentiality. One complication is that the formal structure for what is required under the law and regulations to be submitted in support of a marketing application is different from what has to be submitted under an IND. Requirements for marketing applications are more stringent because, before exposing the whole population of the United States to a drug, the FDA would like to know everything that has been done about that drug. Accordingly, we came up with an algorithm that calls for complete reports of PG studies whether the sponsor wants the results to go into the drug label, or they are part of the database to support approval. With full marketing applications, we also ask for a synopsis of all other PG data, for example, out of a non-validated system, but this could just be a paragraph in the application.

In summary, we hope that the proposed policy steers a path between aggressive regulation of a new field, which might have a real chilling effect on the development of that field, and a hands-off approach to new science that allows that science to develop without interaction with regulators. And we are trying to go further, to encourage an element of voluntary sponsor participation with regulators that is highly beneficial to the agency and the public. We think we are moving in the right direction, we have received a considerable number of comments on the draft, and we will be evaluating those.

We also are anticipating the integration of pharmacogenomic data into clinical use—meaning the product label and so forth. The FDA cannot integrate this new scientific knowledge into a product label unless it has gone through the clinical trials process and application process and that is the next regulatory challenge.

The first way we anticipate appearance of pharmacogenomic information is what we refer to as *informational inclusion* in the label. What do I mean by that? Currently, there is a lot of information on drug metabolism in labels. This drug metabolism information comes mainly from the phenotype of the patient. A person who does not metabolize a drug well will have higher blood

levels than most people. The label for that drug would include information on what enzymes are responsible for this, but that would be strictly from the phenotype. Now, you can do this from the genotype. In other words, you can test a person's genes to determine how that individual metabolizes the drug. The person might be told, "Anytime you get a drug that is metabolized by this pathway, the levels of that drug in your system are going to be too high because you are a poor metabolizer of any drug that is metabolized by this pathway." So they could get a profile, a prediction, that says how they will metabolize drugs.

This type of information will start to get incorporated in drug labels as genetic tests become available. The label provides advice to the clinician. It does not direct the clinician to do one thing or another; it is advisory. When that information starts to be included in the label, we would like to see the related data in the drug application just as we presently see phenotypic data.

So, conceptually, how to handle this new data is not that complicated. The main problem is that patient-specific data often are not crossing over into clinical practice. There are instances when everybody receives the same dose of a drug even though, for decades, there has been a means to predict that certain people are not going to respond to the drug or are going to respond poorly— for example, from a particular painkiller because their system does not turn it into an active drug. They still get that ineffective painkiller, which is a shame.

Pharmacogenomic data in labels will eventually extend to directed therapy, meaning instructions to run a genetic test prior to or during therapy. As this era arrives, we would like to see co-development of the pharmacogenomic test and the drug together so they both reach the finish line at the same time—meaning simultaneous approval of the drug and diagnostic. Clinicians should be able to order the diagnostic test with confidence in its reliability in conjunction with the opportunity to write a prescription for the drug. The centers that regulate drugs and medical devices[15] are working together to issue guidance on how a sponsor might develop both products simultaneously. This is a challenging undertaking, for there are a tremendous number of validation questions. Nevertheless, we are going to try to issue a guidance, which means that we will follow the public process and have a public discussion about what might be required.

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15. Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH), respectively.

Another question, one that is always raised by the firms, is, "What will the FDA do if specific populations are discovered during clinical development?" For example, imagine a drug sponsor that anticipates its drug will be used to treat everyone in the country with hypertension. What happens if the data show that there is a smaller group that has a much greater benefit from the drug, and another at a higher risk from the drug, and so forth? The sponsors' concern is that the FDA will limit the indication to the most responsive groups. And this is where the ethicists, venture capitalists, and everybody else start talking. First of all, recognize that we absolutely support the development of pharmacogenomic-directed therapy. Why? Because this is the future of drugs and therapeutics in the United States if we are going to move beyond empirical drug development.

Second, we have to recognize that this is an area in transition. It is a little premature to worry about the FDA limiting populations when there is no critical mass of pharmacogenomic tests to use in drug development. Frankly, understanding the utility and the limitations of pharmagenomics directed therapies will take some time.   Nevertheless, this is a period of change, which is uncomfortable for many people. It is important to remain focused on the ultimate goal.

Third, we must remain cognizant of the fact that the traditional drug development pathway is familiar, established, and has revolutionized the treatment of many diseases in the United States. Patients are currently enrolled in trials based on biomarkers developed by clinical observation and through the application of traditional scientific methodologies. The traditional pathway may deliver clinical benefits for some time to come, and it is also a solid point of reference for dealing with new science. From the FDA's point of view, whatever patient characteristic is studied, the overall process ultimately is a hypothesis testing exercise.

Fourth, we must acknowledge that there is a tremendous amount of hype involved. The reality is that it takes time and effort to verify the validity of any observed association. At the FDA, we feel this in our bones because we have experienced this process so many times—not yet in pharmacogenomics, but pretty much in all other areas of established medical science.

An occurrence in one trial may not prove to be a repeatable association, and any association may be confounded by a bouquet of variables that lead you down a lot of garden paths. An association that is very statistically significant may arise in a trial but, the next time that or a similar trial is done, the association is not visible at all. So any initial finding in a subset of people, no matter how exciting, must be approached as a hypothesis-

generating event that must be confirmed.   Are there any exceptions? Perhaps.

My personal theory is that cancer treatments must be approached more like the development of antibiotics or anti-virals. Why?   The genome you are testing really is not the person's genome; it is a mutated genome.   You are looking at a gene sequence or expression data in the tumor and trying to individualize, but not to the person as much as to that person's individual tumor.   This theory is linked to specific hypotheses about molecular mechanisms of intervention, based on the molecular mechanism of oncogenesis. Presently, when we look at tumors, we are highly observational—meaning we characterize them as lung cancer, liver cancer, and so forth. We may see a shift from this to treating mutated cells based upon their specific patterns of mutation.

So, cancer treatments may prove especially conducive to pharmacogenomic-directed therapies because we are treating mutated entities within the body.   The concept is going to be applicable in other diseases eventually, but in not as much of a clear-cut manner. Most diseases are not as mutation-based.

How will the advent of pharmacogenomics impact medicinal use of approved drugs? The use of many drugs currently on the market could be tremendously improved by genomically directed therapy. Nevertheless, our experience so far at the FDA is that we are going to encounter considerable push-back from the clinical community on making this transition. The tests are unfamiliar and costly, and the cost-benefit will be hard to elucidate in many cases. To illustrate my point, consider testing for TPMT, an enzyme that metabolizes 6MP, a drug used in childhood cancer therapy, among other indications.   This is a not-so-rare mutation that impedes metabolizing 6MP, and those individuals get extremely high exposure to the drug if they are given an ordinary dose. Accordingly, there has been a push to routinely screen people for this mutation before they are given 6MP.   We formed a public advisory committee on this topic, and the clinical community is really quite conflicted.   They have a long history of success in treating childhood leukemia, and they are worried about the consequences of switching to a genetically tailored dose regimen. In contrast, if you can screen to eliminate people who are at high risk for some horrendous side-effect, I believe that is much more likely to be widely accepted.

Our observation at the FDA at this time is that, outside of oncology, pharmacogenomic-targeted therapy will consist of using genetic knowledge to enrich, rather than to cleanly predict, responses to pharmaceuticals. Most responses are probably going

to be multi-gene driven, and so reliable prediction will not be readily possible.   It is unlikely that you will have very reliable prediction of responses in very small groups of people—a common belief in the basic science community right now.   Consider depression, an extremely variable disease presently treatable with a collection of antidepressants recognized as effective through clinical use. If these drugs are tested against a placebo, they fail to show effect almost fifty percent of the time.[16]   The reality is that we really do not know what depression is. The diagnosis is based on observation, and it likely is a common symptom for a wide variety of problems involving variations in brain chemistry. Pharmacogenomics will introduce deeper understanding, but most likely with high clinical complexity.

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16. Arif Khan et al., *Are Placebo Controls Necessary to Test New Antidepressants and Anxiolytics?*, 5 Int'l J. Neuropsychopharmacology 193, 195–96 (2002).