Transcript of FDA Press Conference on Warfarin

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Moderator: Karen Riley
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Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen only mode until the Question and Answer Period. If you would like to ask a question at that time, please press star then 1 on your touch tone telephone. Today's conference is being recorded. If you have any objections you may disconnect at this time.

I would like to introduce the host for today's conference, Miss Karen Riley with FDA's Press Office. Ma'am you may begin.

Karen Riley: Yes thank you. Good afternoon. Thank you for joining us today for a U.S. Food and Drug Administration teleconference on an important drug labeling change regarding warfarin, a blood thinning drug.

With me today is Dr. Janet Woodcock, Deputy Commissioner and Chief Medical Officer at FDA; Dr. Larry Lesko, Director of the Office of Clinical Pharmacology in the Center for Drug Evaluation and Research, or CDER, at FDA; Dr. Karen Weiss, Deputy Directory of the Office of Oncology Drug Products in CDER at FDA; and Dr. Duane

Reeves, Acting Director of the Division of Medical Imaging and Hematology Products in CDER at FDA.

We're going to begin with some opening remarks by Dr. Larry Lesko.

Larry Lesko: Thank you Karen and hello everybody. Today is a significant event for those who foresee a day when medical care will be tailored to fit the unique genetic make up of every single one of us.

FDA is announcing the new labeling that has been added to the commonly used blood thinning drug warfarin. It explains that certain people are likely to respond very differently to the drug if they happen to carry variations of two of their genes. Clinical studies have shown that patients with these variations may need a lower warfarin dose than patients with the usual forms of these genes.

For decades we've known that the correct warfarin dose can vary widely from patient to patient depending on their age, their weight, their health status and what other foods or drugs they ingest among other factors. Now we know that for some people genetics plays a role as well.

With this information in the labeling, doctors and other health professionals may well decide to incorporate genetic information along with more traditional risk factors in estimating their patients' initial warfarin doses.

Identifying these patients with genetic variations may well improve the safe use of warfarin. After all, the choice of the correct warfarin dose is

important in preventing blood clots and avoiding bleeding especially when patients begin using the drug.

This and other healthcare professional who prescribe warfarin should regularly check to see if the drug is working properly by ordering the prothrombin time test to evaluate the blood's ability to clot properly.

Results are measured in seconds and compared with the expected value in healthy people known as the International Normalized Ratio, or INR. INR monitoring should continue to be the cornerstone of anticoagulation monitoring.

Now this isn't the first time that genetic information has been cited in prescription drug labeling. It can be found in a handful of other labels. This is the second time that such pharmacogenomic information has been cited in the drug dosing information.

The first time was with the oncology drug called irinotecan. However this marks the first time that such pharmacogenomic information has been included in a widely used drug.

This means that personalized medicine is no longer an abstract concept but has moved into the mainstream where it is recognized as a factor in a product used by millions of Americans everyday. Thank you.

Karen Riley: Thank you Dr. Lesko. Now to talk about today's event within the context of FDA's Critical Path Initiative is our Deputy Commissioner, Dr. Janet Woodcock.

Janet Woodcock: Thank you and hello everyone. This announcement today can be seen really I think in context of some of the work that FDA's been doing in its Critical Path Initiative.

We are very interested under the Critical Path in bringing advances of modern science as rapidly as possible to bear on the drug development process. And also, obviously as in this case, into drug safety in that the science of understanding variability of people's response to different drugs.

Under Critical Path for this drug, warfarin, we're continuing to engage in various projects that are going to further evaluate the relationship of the genetic variability that's been identified to the outcomes in patients, and to see how this genetic information might actually fit into the process of clinical care that we have right now.

So we have - are now putting into the label this genetic information that explains some of the variability of warfarin response. But there are a number of additional steps that need to go on -- sort of along the Critical Path -- to figure out what the place of this information is in the care of people taking warfarin.

We are doing this for many drugs. Those drugs that are on the market where this - incorporating this new information in some ways is more challenging -- as well as encouraging users to this time of genetic information and other biomarkers in drug development -- and with the intention of, you know, making drugs both more effective, better targeted and safer for patients.

So we're very pleased, I think, from the standpoint of the Critical Path that this is really a proof of concept. It shows that we can - there's genetic information out there.

It comes from the new science. Tests have - are able to be developed that can identify these gene variants. And we can identify people who have varying responses to this drug.

So thank you.

Karen Riley: Thank you Dr. Woodcock. Before we begin taking questions, let me remind you that today's teleconference is for credentialed press only. Shall we begin the Question and Answer Session now please?

Coordinator: Thank you. If you would like to ask a question, please press star then 1. You will be prompted to record your name.

Our first question comes from David Brown with The Washington Post. Your line is open.

David Brown: Yeah thanks for taking the question. Can you talk a little bit about the - specifically what the gene is; what the gene test is called; how much it costs; whether one needs it more than once in one's therapy; how widely it's available in hospitals and doctor's offices, et cetera, et cetera?

Man: Thanks for the question. We're taking about today two different genes. The first gene is called 2C9. And 2C9 is a gene that's a member of a super family of enzymes that predominantly is located in the liver.

The role of this enzyme is to catalyze the metabolism of warfarin and other drugs. And the rate of metabolism -- or the rate at which a patient may clear this drug -- depends on the gene variance in that gene.

So that gene affects the relationship between giving the dose to a patient and how much warfarin they have in the blood. We call that exposure.

The second gene is called VKORC1. VKORC1 is an abbreviation for vitamin K target sight. It's actually called the vitamin K epoxide reductase complex.

And what this gene represents is the sight of action of the drug and gene variants in that gene affect the sensitivity to the drug. So taken together both of these genes affect the necessary dose and the response of the drug to the patient.

Now both of these genes are also widely available. Most of the major laboratories across the country and many of the local academic laboratories offer these tests together. So when one orders a 2C9 test, one also gets a VKORC1 test in the same request.

The cost of the test is variable. It's going to depend on the specific laboratory. And prices of that have been quoted range from $125 to $500. The test itself is only done once. And once somebody knows the gene variants -- if there are any on a patient -- then those are the variants for life.

Karen Riley: Thank you. Next question.

Coordinator: Joanne Silberner from NPR your line is open.

Joanne Silberner: Yeah hi - two questions related to the same issue. And that is what kind of affect this would have specifically for warfarin if it were used every time what would be the difference be? And also if you have anymore global estimates for pharmacogenetics or genomics in general.

Man: I'm sorry could you repeat the first part of that question. I heard you say…

Joanne Silberner: Yeah the first part is, you know, have you - do you know the extent of damage that's done by accidentally incorrect warfarin dosages? And what would happen if every single warfarin dosage was always the correct one? And then more globally have you looked at the whole field of pharmacogenomics and come up with any sort of global measures across the field?

Janet Woodcock: Yeah this is Janet Woodcock. I would say that that's one of the questions we have yet to answer. There are going to be some randomized trials that look at using the genetic information in addition to what's done now versus just doing the standard care. And that is directed to answering the kind of questions you're asking.

I think the point is that doctors have figured out a way to try and get to the best dose of warfarin. And what they do is a trial and error when they start the dose.

And every patient has to come back. And they have multiple tests done. And then the dose is adjusted and more tests done and dose

adjusted. And so they've worked around this variability up until this point. That's been the workaround.

Some of the variability of course is due to diet and other factors that are not related to genetics. So we have to test how good it will be to use genetic information versus the current methods which are, you know, not perfectly satisfactory but work to initiate warfarin therapy. And then we'll have answers to those questions.

Joanne Silberner: Okay.

Janet Woodcock: And the second question I don't think anyone knows the answer to. We're just beginning, you know, the human genome was only sequenced fairly recently.

We know that people -- you know this. Everyone on this call knows that people respond differently to the same drugs. And that isn't just by chance.

There's a reason, a scientific reason. Some of that reason is genetic and some of the reasons are, you know, what happened to your environment, what you eat and so forth.

And the question is what part is genetic and can that help us make drugs safer and effective? And in fact that's what a number of these Critical Path projects that Dr. Lesko's working on and others are working on right now are seeking to find out.

For example, the bad side effect - some people get bad side effects from a lot of drugs. And this may be because their genetic makeup is

such that they either need lower doses of drugs or they're prone to getting side effects for other reasons. And we think we can now find that out.

Joanne Silberner: Thank you.

Karen Riley: Thank you. Next question please.

Coordinator: Andrew Bridges with The Associated Press your line is open.

Andrew Bridges: Hi. Two quick questions. Can you quantify how important the gene test would be relative to a patient's age, weight, diet and all those things in determining the correct dose? I mean would this be the sort of dominant thing looked at?

And then also what has the FDA learned from this study that began from (unintelligible) last November looking at the 800 or so patients. What was the outcome or what have you learned from that study to see if the gene testing…

Larry Lesko: Hello.

Karen Riley: This is Dr. Lesko.

Andrew Bridges: Dr. Lesko, thanks.

Larry Lesko: Well the first part of your question is the relative contribution of various let's call them intrinsic or extrinsic factors -- things associated with the patient or the environment.

The way people have subdivided the variables and their influence on warfarin has been by looking at the dose and the variability in response. And the response in this case is defined by the INR.

In terms of the patient demographics, the predominant risk factor is age. Age is an independent factor that the older one is, generally the lower the dose needs to be. So age accounts for anywhere from 10 to 15% of the so-called variability.

Body weight, body size and other things that are inherent to the patient contribute very little more than age. The reason that genetics becomes important is the percent of contribution that it makes to the overall variability in the dose and the response. It's estimated that 35 to 50% of the variability in dose to response is described by the two genes that we're talking about today.

So the way the information ought to be used is to be incorporated into all of the information that affects warfarin. So that combination of age and any other factors along with genetics would be the best approach we know of right now to figure out the initial dose of warfarin.

Of course once the initial dose is started and patients continue into the maintenance phase, the INR monitoring becomes the major determinant of controlling the anticoagulation dosing.

Karen Riley: Thank you. Next question please.

Andrew Bridges: Wait, wait, wait. I had a second question.

Karen Riley: Okay go ahead.

Andrew Bridges: I had asked it before. What about the study that was done I believe back in November looking at the 800 patients? What has the FDA learned from that?

Larry Lesko: That study was postponed because of some funding issues. It was actually never conducted. So we have nothing to really say about it. It was a planned study that we're going to start with Kaiser. And we did not start the study.

Karen Riley: Is that sufficient Andrew?

Andrew Bridges: Well I guess - without that information you still feel confident in moving ahead then with this recommendation? Because I…

Janet Woodcock: Yes this…

Andrew Bridges: …mean that study - if I understand correctly was designed specifically to look at outcomes. You know, whether it indeed did make a difference.

Janet Woodcock: Right. This relabeling - and Dr. Reeves and Dr. Weiss are on the phone and can talk about it. This labeling is not directive to doctors that they should use this.

We will await the results and outcome study for that type of label if, in fact, the data, you know, show that it is really necessary for the drug used safely.

These - this information in the label is more informational to doctors. It is - it explains some of the sources of variability in the drug response. So there's several steps down this pathway.

We think putting this information and this action we're taking today is really going to stimulate the investigation and getting the conclusions about what the role of genetic testing is at this point in the use of warfarin therapy.

Karen Riley: Dr. Reeves would also like to answer that question.

Duane Reeves: Yes, yes thank you. This is Duane Reeves. As Dr. Woodcock and Dr. Lesko were saying there's much research -- much clinical research -- that remains to be done.

And the information in the most clinically applicable portion of the label has not changed with respect to the recommended dose or the monitoring procedures for the use of warfarin.

What is available is that the language in the precaution section provides one of the many tools that the physicians consider when they select one of the recommended doses. But the actual recommendations for dosing -- as well as the recommendations for monitoring patients -- have not changed.

Larry Lesko: We also…

Karen Riley: This is Dr. Lesko.

Larry Lesko: Dr. Lesko speaking - we have under our Critical Path Initiative studies from the University of Utah that was a study intended to look at the impact that genetic factors might have prospectively on the dosing of warfarin.

This study had indicated that first it was feasible to conduct randomized trials of (VK) based dosing of warfarin. It also established prospectively a superiority of the pharmacogenomic (guide that worked for) dose selection. So that was one of the clinical studies that was done not so much in lieu of the FDA study but in addition to.

Also there was a study that was done at the University of Alabama and was published about two weeks ago. It was a prospective study of looking at the evidence that a variance in the 2C9 gene had a link to the risk of major hemorrhage.

And that study has been published and they found that there was association prospectively in a two year outcome study between the risk of hemorrhage and the 2C9 genotype.

Karen Riley: Thank you. Next question please.

Coordinator: Anita Manning with USA Today your line is open.

Anita Manning: Hi I'm sorry. My question has been answered. Thank you.

Karen Riley: Okay thank you. Next question.

Coordinator: Catherine Larkin with Bloomberg News Media your line is open.

Catherine Larkin: Hi thanks so much. Actually I just wondered if Dr. Lesko could talk a little bit more about the existing drugs for which genetic testing is included in the labeling.

Larry Lesko: Yeah. The - first of all there are many drugs for which genetic information is included in the labeling. But traditionally much of that information was descriptive and was found in the clinical pharmacology section of the labels. And it oftentimes had no bearing on the use of the drug in most cases.

However more recently as information as become available on the molecular basis for adverse events, we've begun to look at older approved drugs to see if their benefit risk profile could be improved through the inclusion of genetic information.

So over the last four years we've updated the labels of several previously approved drugs. The first of which was 6-Mercaptopurine - drug of choice frequently for a leukemia -- especially in pediatric patients. (Azathioprine) - both of those drugs are metabolized by a TPMT gene which has polymorphism similar to 2C9. And both of whom require lower doses for optimal benefit risk.

We've subsequently moved on to another drug in oncology - irinotecan. Irinotecan is a drug indicated for colon cancer. And there's a subset of a population defined genetically that's at high risk for the adverse event of severe neutropenia.

Most recently and last October we also looked at the drug and oncology tamoxifen, and began to explore the question that genetic variance in the metabolizing gene called 2D6 has an impact on the

conversion of the drug to an active metabolite. And it may be such that those patients would not respond optimally to that drug.

That's looked - that's being looked at very carefully now with the data we have and the data we've done since October. So that's one that we're considering.

So warfarin becomes the next in line. And in all of these cases the difference between the more traditional inclusion of pharmacogenetics and these latter cases is that the information has been linked to adverse events in the precaution section, for example, as it was for warfarin. Or it's been linked to some recommendation to consider the possibility of lowering doses of these drugs.

In the irinotecan label we did recommend a specific lower dose for the patients that had a UTGT variance. And that was about as directive as we've been able to get in the various labels I mentioned.

Catherine Larkin: Thank you.

Karen Riley: Yeah - we're going to have another - Dr. Weiss is going to answer.

Karen Weiss: Just a - this is Karen Weiss - not exactly along the same lines but somewhat related there have been a number of drugs that have been approved for oncology settings.

Examples include Herceptin and Erbitux that are both therapies that are used to treat certain types of cancers. And specific testing of patients' tumor types help direct what patients are most likely to respond to the therapies.

Karen Riley: Thank you. Next question please.

Coordinator: Next question is from Robert Bizelle with NBC News, New York. Your line is open.

Robert Bizelle: Thank you for taking the question. Could you just tell us exactly what the label does say about whether the doctor and how the doctor should consider using the tests?

And is there any thought given to increased tort liability for doctors who don't give the test now that it's on the label and the patient ends up having a side effect.

Karen Riley: This is Dr. Reeves.

Duane Reeves: Hi this is Duane Reeves. I'll talk about the first part. With respect to the major clinical portions of the label are the alterations are in the precaution section. There's two paragraphs specifically that are somewhat altered in the precaution section. And one of the key words in there is the word may in this precaution section alteration.

And I'll quote the change verbatim. In the period determination of the PT and INR the label change notes that numerous factors alone or in combination including changes in diet, medications, botanicals and genetic variations in the CYP2C9 and VKORC1 enzymes may influence the response of the patient to warfarin.

And then in the other section of the precautions, there is quite a list of the factors that prescribers need to consider when they're prescribing

warfarin that - both the initial dose as well as how to subsequently adjust the dosage. A number of these factors are relatively subjective. For example, debility, diet if you will.

And the label as been altered in this change to identify these laboratory tests as just another one of the potential tools the doctor may consider in prescribing warfarin.

Specifically it says identification of risk factors for bleeding and certain genetic variations in CYP2C9 and VKORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses.

And then in the dosage administration section to reiterate what I said earlier, the recommended dose -- the initial recommended dose -- is a dose of 2 to 5 milligrams. As you can tell there's an option varying between 2 up to 5 milligrams per day.

The text -- the modified text -- says that the lower initiation dosage should be considered for patients with certain genetic variations in CYP2C9 an VKORC1 enzymes as well as for elderly and debilitated patients. And again the label gets into the more subjective factors.

So, if you will, these enzyme genetic tests that we're talking about today they provide somewhat more of an objective tool that physicians can use in their many considerations of choosing the dose.

The label does not say that performance of these tests is required. And in fact I think the label emphasizes to a certain extent the unknowns

with respect to the importance of these factors in ultimately impacting outcomes.

Karen Riley: Thank you. Next question please.

Coordinator: Sue Sutter with Scrip World Pharmaceutical News your line is open.

Sue Sutter: Hi. Thanks for taking my question. I apologize if this has already been touched upon a little bit. But can you explain the role of the Critical Path Institute in all this? I mean I was - it was my understanding they were working to develop a genotype driven dosing algorithm. And is that work still ongoing? Thank you.

Janet Woodcock: Yes they are working on that. And we - there are a variety of groups that are looking at this. The C-Path Institute and the work that's been done there has given us some valuable input which Larry referred to earlier.

But as we said there's a fair amount of work that would have to be done before the biomedical community would determine whether or not this would be considered part of standard therapy or not. As Dr. Reeves as already explained, this is right now just one of the factors to consider when dosing warfarin.

So we hope under Critical Path that we will continue to collaborate with a number of groups -- including the C-Path Institute and University of Utah -- in nailing down the level of contribution of genotyping to management of patients who need anticoagulation.

Karen Riley: Thank you. Next question please.

Coordinator: (Max Coccus) with Federal News Radio Washington your line is open.

(Max Coccus): Thank you. My question is - it's probably a little bit more nuts and bolts but I'm trying to understand how large a universe are we talking about of people who are taking warfarin does this labeling change effect?

And was also wondering what, if any, in particulars did you find in the research that prompted you to make this change and effected your decision to make this change? Thank you.

Larry Lesko: So the question may have revolved around how many people actually have a gene variant of 2C9. And that amounts to about 35% of people that have one or more variants in the 2C9 gene. That means 70% have what we might call normal genes.

Clinical evidence that's both cited in our label and in other releases from the FDA primarily focus on the relationship between the gene variants and the final maintenance dose in patients. It also focused on INR control which is important as a prerequisite to either optimal - or suboptimal therapy.

So again the clinical evidence from a combination of retrospective observational and several prospective trials was that gene variants are associated with better INR control and lower doses than the usual 5 milligram dose. It was that type of evidence that led to consideration of the label update.

As Dr. Woodcock has mentioned, we did have to stop short of recommending specific doses for specific genotypes. And that's the

type of additional information that studies that would be conducted (under) Critical Path that would really focus on.

Now on the other gene - the VKOR - the variants in the VKOR gene are actually a little bit wider than with the 2C9. And there is a racial or ethnic difference in the distribution.

Most of the information we have are on Caucasians. And roughly 60% of Caucasians have at least one variant in that gene. In terms of African Americans, about one in four have a variant in that gene. And in Asians about 80% have a variant in that gene.

So there are some ethnic differences. And the differences will be reflected by the population. And there will be some differences between 2C9 and VKOR.

So in interpreting the data, what physicians and patients have to think about is basically the number of gene variants in a given patient for both the 2C9 and VKOR. The larger the number of variants, most likely the lower the dose and the potentially higher risk for adverse events or for INR control.

Karen Riley: Thank you. Next question please.

Coordinator: Deborah Levinson with Clinical Laboratory News your line is open.

Deborah Levinson: Hi thank you for taking my questions. I actually have a related group of questions the first of which is will the warfarin label refer at all to dosing algorithm?

And I'm also wondering if the FDA is involved at all in efforts to educate physicians about the use of these tests given the new label language.

And I'm also wondering too if you can comment on the role of the ethnic makeup of a population served by a physician or a hospital and the use of these tests.

Larry Lesko: So I'll start and people can add.

Karen Riley: This is Dr. Lesko.

Deborah Levinson: Okay.

Larry Lesko: So in the first part of your question you talked about a dosing algorithm. And a dosing algorithm by definition includes a set of genetic and non-genetic factors.

Such algorithms are available in the literature. There's at least one algorithm online that was published by Dr. Gage and is available to physicians on the Internet called www.warfarindosing.org. And there's a database behind that.

Deborah Levinson: Okay.

Larry Lesko: But that's an example of an algorithm. It's not the type of thing we were comfortable putting in the label at this point because these algorithms were developed and based upon specific populations by the investigators that studied them.

So what we've actually asked people to do that have developed algorithms is expand the patient database to include exactly what you said in the second part which was a more diverse population to see how effectively they would work.

But long-term algorithms would be attractive because it's a way to integrate genetic information with age, body weight and gender and any other factor that could influence the dosing of warfarin.

Now with regard to the other question about education. We have a number of things going with education. First of which is we're working with the AMA and the C-Path Institute.

And this refers back to Dr. Woodcock's Critical Path Initiative. And the purpose of that collaboration is to develop a brochure that could be provided to physicians and patients to explain genetic and non-genetic factors and how they relate to the dosing and monitoring of warfarin.

We're also working with our Center for Devices in constructing a warfarin video that we would make available on the Web site. We've already done this for the irinotecan. And it appeared to be very effective in sort of educating physicians and others about the genetics of the drug and the use of the test.

So a number of those educational things are really in progress. And we'll probably have more than what I just described there.

Deborah Levinson: When do you expect these resources to be available - the brochure that you're doing with AMA and the video? Are those something that

would say be available in the next couple of months or are these more in the future?

Larry Lesko: Well we are currently reviewing prototypes of these educational materials and they look very good to me. My expectation would be that these would be available in the last quarter of this year after they undergo appropriate review. But at this point in time they're fairly mature.

Deborah Levinson: Thanks.

Karen Riley: Thank you. Next question please.

Coordinator: Lisa Richwine with Reuters your line is open.

Lisa Richwine: Hi. Thanks for taking my question. I just wonder if you could talk a little bit more about how this label change originated? I mean often you have a drug maker will propose a label change.

But that doesn't sound like it was the case here with. Was something generated internally through the Critical Path Initiative? Or I'm wondering did some of the testing companies lobby for it?

Larry Lesko: Yeah I think -- and again others may want to answer this question -- but the interest in this drug it was well known for a long time that it's both widely used and causes bleeding. That had been corroborated by many sources.

The Office of Drug Safety here at FDA in 2003 had done a survey of adverse events using the FDA database as well as the published

literature and found that along with the increase in use of warfarin over the years -- and it was reported to be 45% increase over a six year period from 1998 to 2004 -- the drug consistently was in the top ten for the largest number of serious adverse events. In fact in many publications it's responsible for 15% of severe adverse events.

So the (unintelligible) database at FDA was also looked at and it was the second most popular drug in the early part of the 21st century -- the years 2000, 2004 -- in terms of causing adverse events.

It was also the second most common in hospitalized patients related to adverse events. So taken in total the use of the drug was associated with the risk.

The FDA has recently published that paper describing that adverse event evidence. And Karen could maybe provide that later as a reference. It was published in July.

But the look at what the risk factors were contributing to this adverse event profile really led us down the path to the relabeling. When one began to look at the risk factors that Dr. Reeves had mentioned, they did not in and of themselves seem to associate with this high percentage of adverse events.

And then as new technology became available to look at the genetic makeup of patients, it became evident that there was ample evidence to suggest that genetic differences along with the other factors contribute to, we think, the adverse events rate.

Lisa Richwine: But did you hear of any testing companies also who wanted (this)?

Larry Lesko: Testing companies did not come forward and say we want this test. We were interested primarily in the clinical usefulness of the tests. And I think testing companies would be interested in what FDA and others think about the use of genetics before they would step forward.

That being said in many institutions such as Mayo Clinic, Harvard - these tests have been offered for some time in the academic environment in association with research that investigators have been conducting. There appears to be some demand for the tests even before today by virtue of the fact that almost all of the major commercial labs have offered this test to their clients.

Lisa Richwine: Okay thanks.

Karen Riley: Thank you. Next question please.

Coordinator: John Wilkerson with FDA Week your line is open.

John Wilkerson: Who makes the genetic test? And is it FDA regulated or CLEA regulated?

Larry Lesko: There - well many people make the genetic tests. They're oftentimes referred to as laboratory developed tests. They're often manufactured by companies including companies like Kimball Genetics, (unintelligible) and others.

At this point in time none of these tests have gone through the approval process at FDA. Although several of them are under

consideration. And other companies have publicly said that they intend to submit applications to FDA.

That being said when these tests are utilized -- these lab prepared tests are utilized in patient care -- they are regulated in terms of their quality and in particular their analytical clinical validation quality by CLEA regulations under the (CMF).

John Wilkerson: Did any of the drug makers offer to help pay for the clinical trials that have been done or are proposed to be done?

Larry Lesko: Well the drug is off patent so there are many drug makers - there's the original brand name Coumadin and many generic companies. But to my knowledge they haven't stepped forward to offer to pay for the - conduct clinical trials.

Karen Riley: Thank you. Next question please.

Coordinator: (John Rikert) with Congressional Quarterly, your line is open.

(John Rikert): Yes thanks. If I'm understanding you correctly if a doctor knows you have these genetic variations, he or she won't be able to adjust your dosing yet. So what is the practical, clinical significance of this announcement? And also how soon will this data be available to allow doctors to adjust doses?

Duane Reeves: This is Duane Reeves. There may be some misinterpretation there. Again this labeling recommendation does not change how physicians alter their dosage in response to (ET) INR results, if you will. In fact

none of the recommendations for either the initial dose or subsequent dose of - have changed in the label.

What this label change does is that it highlights, if you will, the availability of these tools - these tests for the physician to test their patients. If the patients have an allele genotype with these variations then it behooves, it's logical in the practice of medicine to use the lower initial dose. As I had mentioned earlier the recommended initial dose is somewhere between 2 to 5 milligrams.

For example as it stands right now a physician could use very subjective factors in trying to determine whether my patient is debilitated, if you will. As you can imagine debilitation is open to many interpretations.

But candidly the process of medicine in the dosing of warfarin right now involves a great deal of subjectivity. And this has been mentioned -- we have a sizeable number of adverse (warning) events, if you will -- that are likely related to some of the challenges in selecting this initial dose as well as subsequently adjusting the doses.

The genetic testing importantly impact the choice of this initial dose whether it's to start the patient on the low end, if you will, the 2 milligrams or the 5 milligrams. And that is an important consideration during this very first few days of starting warfarin therapy.

Subsequent dose adjustments after the first few days are based on PT INR results. And again to reiterate the dose adjustment paradigm has not changed.

(John Rikert): Okay.

Karen Riley: Hello Dr. Lesko would like to add something please.

Larry Lesko: Yeah I think I'd like to emphasize again what Dr. Reeves said. And I think the way that (we) thought about genetic testing along with the other risk factors is that they provide an objective tool to stratify patients.

So if you take all patients who are intending to go on warfarin, the relative risk and the anticipated maintenance dose of this drug is going to depend on these risk factors.

So for example if a patient was over 70 years of age versus less than 50 years of age, that would be stratifying the patient on the basis of their dose requirements -- or at least anticipated dose requirement -- and a relative risk of having adverse events.

Likewise the genetic tools that Dr. Reeves mentioned allow physicians to stratify patients the same way based on their ability to analyze drugs and their sensitivity to the drug.

(John Rikert): But did you also say that we will see additional data, you know, guiding the physician on dosing. Could you just explain that again please?

Larry Lesko: Yes. I think Dr. Woodcock alluded to this. And the fact is there are many studies being conducted now to develop the dosing algorithms for warfarin.

You know, the expectation is that these studies will continue to be conducted. And we're going to look forward to the results of those studies to develop what ultimately I think would be useful to physicians and that is a dosing algorithm that allows them to integrate information about genetics and also about the demographics, age and weight of the patient to make it simpler to adopt these tools into clinical practice.

Karen Riley: Thank you. Next question please.

Coordinator: (Mark Bloom) with MedPage Today your line is open.

(Mark Bloom): I'm curious why with all the - with all you have said today that the label change does not recommend the use of these tests for - at least for patients who are likely to need warfarin. It merely highlights these tests. It doesn't urge that the tests be used. It doesn't recommend that they be used. Why was that not done?

Duane Reeves: This is Duane Reeves. Again this somewhat gets back to some of the items we have been talking about. At the - there is a considerable amount of information available today to suggest that the presence of these variations importantly impact the choice of the initial warfarin dose as well as the propensity to bleeding.

On the other hand, the clinical data available today are not sufficient in our judgment to actually alter the recommendations in the label such that we require, if you will, or even strongly encourage beyond what we have described here in the current label the use of these tests.

Again there are so many considerations. The subsequent clinical tests may actually prove to show that these tests are essential, if you will.

And if the data do turn out that way we anticipate the labeling will be promptly changed to reflect that.

But right now we're balancing some of the considerations which we know right now importantly impact the safety aspect of this against some of the - what we don't know about the tests and their use in clinical medicine.

Hopefully over the next few years we will have more definitive information such that we can really optimize the use of the tests. I think we're seeing right now just the early stages of the use of these type tests in clinical practice here. And it represents an exciting chance.

But again we're not quite to the point where we can say that doctors must perform these tests, if you will. Doctors still can practice good medicine without necessarily doing these tests. But the tests are available. And that is one of the major points that we hope to make with making the change there.

For example you can tell the warfarin label we highlight many of the factors that doctors should consider. There's quite a list of botanicals, if you will. And the objectivity within these tests is probably much more substantial than some of the objectivity in determining whether or not a botanical impacts the response to warfarin.

(John Rikert): But if…

Karen Riley: Dr. Lesko would also like to make a comment.

Larry Lesko: Yeah in addition to what Dr. Reeves mentioned, I wanted to make the point that requiring a test in the label must have as a prerequisite assurances that the test is widely available to physicians.

You wouldn't want to put any doctor or any patient in a situation where if a test was required and they didn't have access to the test. And I don't think we're at that place yet.

We'll have to see -- along with the additional data -- whether these tests become widely available with a quick turnaround time. And this is going to be an aspect of the framework for additional testing.

In addition we've encouraged the diagnostic industry to submit for consideration by FDA the approval of these gene tests. And we hope that companies give this some serious thought as we move forward as well.

(John Rikert): Well don't you think that as the results of this press conference there is going to be a great demand for these tests and that you really want it both ways? You're saying hey these tests are here, but we don't know whether you should use them or not?

Larry Lesko: I think again as Dr. Reeves said the language in the label is important. I think we felt an obligation to share the information that we have and the level of evidence that we had.

And basically what it says a physician may want to consider these tests. Physicians may approach this very differently depending on their experience with their patient population and so on and so forth.

We do know though from the adverse event literature and from other reports that the drug is problematic and people may view this as part of the solution to better management of INR control and so on.

Karen Riley: Thank you. Moderator we have time for two more questions.

Coordinator: Thank you. We have a follow up from David Brown with The Washington Post. Sir your line is open.

David Brown: Yes I just want to get back to the genetics a little bit. I take it there are a number of different variations -- alleles -- for both of these genes and that one can be sort of homozygous or heterozygous for these various alleles that, you know, causes greater sensitivity so that they can pile up. And first of all is that correct?

And can you give me some sense of what the - if you have all of the available alleles how much lower your dose or how much greater your sensitivity is and whether people with those dangerous profiles in fact have a greater hemorrhage rates and, you know, there are studies showing that.

Larry Lesko: Yeah I think there was a good example of that in The Wall Street Journal article saying that started off with a case study about a patient that had actually all of the at-risk alleles in their 2C9 and VKOR and was administered 10 milligrams of the drug and ended up needing 1 milligram.

In fact we have data from pharmacy benefit managers that up to 1/2 the patients who are started on 5 milligrams end up with different doses -- and in most cases lower doses -- of warfarin.

So the worst case is related to the number of gene variants one has. With respect to the 2C9s, the most sort of severe case would be somebody that has two gene variants that we call star 3/star 3.

As you mentioned they're homozygous and they basically have only 20% of the activity of that 2C9 gene. So somebody that was quote a star 3/star 3 or a person that had two gene variants -- one from their mother, one from their father since there's two copies -- would be most at risk.

Now there's going to be people at intermediate risk that might have one gene variant. But the number of gene variants will effect the eventual maintenance dose in many cases.

Now on the VKOR gene one could have either one or two gene variants. So if you add those up, a given patient who gets tested for 2C9 and VKOR will have anywhere from zero to four total gene variants for each of these - for this combined test between 2C9 and VKOR. And as the number of the variants goes up so does the risk and the potential lower dose.

David Brown: Okay thanks.

Karen Riley: Next question please.

Coordinator: Joanne Silberner with NPR your line is open.

Joanne Silberner: Hi thanks. You mentioned that the PT test takes just a couple of seconds. How long do these tests take?

Larry Lesko: These tests are very quick. It takes a little bit longer for a patient to get the INR done. But basically I think the tests are minutes when they're actually done in the laboratory.

((Crosstalk))

Joanne Silberner: The gene test so you could go to the doctor and they'd be able to test you right there?

Larry Lesko: Did you ask about INR or genetic testing?

Joanne Silberner: Genetic testing.

Larry Lesko: Oh okay I'm sorry. I thought you said INR. Oh so genetic testing is going to depend on the setting. If you're at a major medical center where these tests are run -- I would say frequently and more in volume where there might be patient care and research being done at the same time -- the turnaround time on these tests could be one day or less.

If you're dealing with a commercial laboratory where a blood sample -- and it has to be a relatively small blood sample -- is sent out to a laboratory by a physician or by a clinic it might take anywhere from three to five days to get the results back.

So the range really depends on where the practice is and what the frequency is of people using the test to begin with.

Joanne Silberner: Thanks.

Janet Woodcock: I might add Joanne that of course you only take one genetic test. But the INR tests are repeated and then there's travel time and so forth if you want to…

Larry Lesko: Right…

Joanne Silberner: Right.

Larry Lesko: …so the - I think the whole goal of warfarin therapy is to get INR control as quickly as possible. That means thinking about the risk factors that are going to effect the eventual maintenance dose of the drug. The more of those one knows the quicker one might get to the target INR.

And there is a bit of inconvenience in terms of INR monitoring especially for older people, people living by themselves that have to get in the car, drive to a clinic, get a blood test done and maybe come back in five days to repeat it as the dose is changed or fluctuates.

So one of the benefits of testing in terms of understanding this risk factor early is to get to the maintenance dose that's optimal for that patient quicker.

Joanne Silberner: Thanks.

Karen Riley: Thank you. This concludes our media call on the drug labeling change for the blood thinning drug warfarin. And I want to remind you that a replay of the call will be available one hour after this call concludes through August 19.

And if you have any questions about today's event, please contact me, Karen Riley, at 301-827-6244. Or alternatively you can email me at: karen.riley@hhs.fda.gov. Thank you.

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