



## AMDA Conference Call Transcript

### Session No. 9: 2nd FDA Teleconference

**Speaker: Dr. John Hyde, Medical Team Leader at the FDA**

**Date: Thursday, January 27th, 2005**

I would like to introduce Dr. John Hyde. He graciously agreed to come and answer all of our questions. I am going to give a little background.

He received his PHD in statistics from Stanford University and got his MD degree from the University of Miami. Dr. Hyde joined the FDA 13 years ago and since then he has been involved in the review and approval of wide range of medical products including drugs for treating addiction disorders, analgesic drugs, arthritis drugs, clinical laboratory devices, and cardiovascular devices. Dr. Hyde is currently the team leader of the vision of therapeutic, biologic and internal medicine products where he has been responsible for over-seeing the review of a variety of biologic products, including those used for treating inborn errors for metabolism. Welcome Dr. Hyde and thank you for taking the time.

Well thank you. Ok there are several questions you supplied, but I thought it would be helpful if I go over just sort of an overview of what the FDA does and the drug approval process, actually the drug development and approval process. I think it will provide sort of background on context and then we can go through those specific questions and then fill in what is missing there.

#### **Q: How big is the FDA facility?**

**A:** There are about 10,000 people. It includes several different sections and it really involves several different aspects of the economy. There's a center for foods, center for veterinary medicine, center for toxicologic research, a center for devices; it covers everything from Band-Aids to artificial hearts, a center for biologics; which is vaccines, blood banking, gene therapy, and then the center for drugs which is about a third of the FDA personnel, I believe. It is probably the largest center in there.

Most of the people at the FDA, that work here outside Washington, but there is certainly a large number that are in field offices throughout the country; doing inspections or working on enforcement actions.

Before I get started, just an issue about confidentiality. Most industries when they have product ideas or products under development, research consider that to be trade secret information, but because pharmaceutical research and development involves experimenting with human subjects, they are subject to special regulations and a high degree of oversight. So then they are required to submit information that would usually be considered trade secret to the FDA so we can exercise our oversight function, but as sort of a compliment to that we have to keep that information confidential. I'm not allowed to then discuss products that are under review. Some companies make that information public if they choose to, but others keep want to keep it secret for variety reasons and so we have to respect that confidentiality; so I really won't be



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able to talk about anything specific that hasn't been approved.

As we go along, you know there is a lot of lingo and drug development, so if I say anything that is unclear it is perfectly fine to interrupt and ask for a clarification as we go along. I may sort of lapse into the lingo as part of this.

First of all, I will have to simplify things because there are certainly a lot of special cases and exceptions and I can't go into all the details, but I will try to present a more or less generic scenario for how a drug is developed and what the FDA does during that process. The FDA doesn't do any of the studies itself. These are really done by the company. They do all the testing of the manufacturing facilities, laboratory studies, animal studies, clinical studies, by themselves. So the FDA doesn't do any of the drug evaluation per se, but it does review all that material that the companies provide to us. The FDA has its hands in it really much of the way and we're not just sort sitting there waiting for everything to get done and then they submitted to us for an approval really very much involved in many products all the way from the beginning of drug development to the point where it finally gets submitted to us for approval.

If you look at the food and drug law, it starts out by saying you can't distribute a drug unless it has been approved by the FDA. So then the question is how do you study an unapproved drug, and the law allows for a special exemption, which they call the investigational new drug exemption and it's called (IND) for short. So I am going to be using that term cause it's sort of common term the IND. You can sort of think of it as a license to investigate a drug. You don't get any certificate to hang on the wall, but we just open a file for you, but that is how the drug development is done under an IND, and what it does is lets the company distribute the drug and give it to subjects as long as they follow certain procedures.

Now, large company can have several INDs for different products or sometimes even for the same product if they are looking at it to treat different diseases they'll have different INDs going, but a small company may just have one for their main product. All studies of the drug, before it gets approved anyway, are done under the IND and the FDA keeps a file on the drug development program and it's not just a manila folder. We're talking often volumes and volumes of information that the company will submit during the drug development process.

Now, to get one of these INDs going the company has to submit results of their testing on the product, it covers sort of basically three things, the product manufacturing process, results of any animal studies they've done already with the product, and then their proposal for what to do for human studies, and when the FDA gets this information it has 30 days to decide whether it is ok to go ahead with the program or whether they need to put what we call a hold on it. We tell them they can't start until they either submit certain information or make certain changes to their program. Now this information is usually reviewed by a team of product reviewer who is usually like a PHD chemist or an immunologist, another expert in animal studies, maybe a PHD pharmacologist or a doctor of veterinary medicine or sometimes a physician, and also a doctor that looks at the clinical protocol to evaluate the light of all the other information.



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As I have said, the FDA has 30 days to decide that they have to stop the study or actually not start the study, but usually what we'll try to do is if we see a problem we will try to work with the company and try to get whatever additional information or ask them to change their plan in a way that makes it acceptable. So it is unusual that we would actually have to tell a company not to go forward, but that is an option if we don't think that it is safe to do so. Now sometimes it is an IND, for a new drug this might be a first time it would actually be used on humans. Sometimes it is a drug that has been used elsewhere before, but sometimes it can be a little scary. The first time it goes into a person you haven't had that experience before. So we have to rely what we have learned in animal studies to try to decide what's the safe dose to start out at and what sort of monitoring might be necessary, but I think it is a testament to the system that really misadventures are really exceedingly rare.

Are there any questions up to this point? No.

Ok.

Now the drug is often in this IND phase for many years and people both at the FDA and the drug company may change over that period of time, although, we usually try to keep one person on it so that they are familiar with the product. Now every time a new human study is done with that product a protocol has to be submitted to the FDA and at each point we have the option of deciding if we don't think that it is safe of putting that study on hold. Usually those studies go through several phases, usually the first studies going to be just like a single dose study to see what happens, starting at very low doses and then going progressively higher looking for any problems with safety, if things look good at that point they may go, that is usually called phase 1 and then the next step is called phase 2 studies, then there they may try to give it for longer periods of time and also try to use it in patients to really see if there is going to be a therapeutic affect. Try to figure out what the best dose is, what the dosing interval and sort of fine tune it, really learn what their drug can do and how best to use it.

That phase may actually last for quite a while for some drugs certainly for common diseases there may be various ways they want to try to investigating it, but for rare diseases where you have only a few patients that stage may be fairly limited and you may want to move more rapidly, on to what is known as phase 3. And phase 3 is when the company is doing really its main studies that would support an application for approval to the FDA and usually what we set up the standard is two well controlled i.e. some important comparative group often a placebo controlled, but other possibilities are used sometimes too with the purpose of demonstrating that it really has a beneficial clinical affect. In further evaluating whatever safety concerns there may be for it, and they really try to get it tested under more or less realistic conditions i.e. not a very select patient population, but you know everybody that might reasonably be treated with it or at least put the population of people the company would hope to have it indicated for.



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**Q: How does the FDA define an official affect?**

A: That varies and for some things it sort of a condition that may affect many other treatments already there is sort of a standard is to what is considered significant or beneficial affect. For other things that are more novel, it can be a little more difficult because there may be no real standards or studies that have been done before that really define what that is. We sort of have the approach would be that we really like to have it be a clinically meaningful affect. So that in most cases showing a laboratory parameter changes something isn't usually a sufficient indication of benefit. We like to see something that patients can really recognize as being "I'm better in this way or that way." For certain things, like blood pressure treatment though. Blood pressure is used as the indicator of affect, but in that case there is a pretty long track record an established benefit of lowering blood pressure. As we get into areas where less maybe known about it, we usually fall back on stuff that we can talk about clinically. At the same time the company may also be doing additional animal studies, there maybe although human data, human studies are really the most important thing for deciding the safety and effectiveness of a drug. There maybe other questions that we need other animal studies to address like does it cause cancer, what's the effect on pregnancy those are the things that maybe carried out as animal studies and would still be important things to know.

**Q: When is it appropriate to use a surrogate marker, I'm thinking like a clearance of a sub-straight for lysosomal storage disease, is that considered a surrogate marker and is that something that would be considered clinically meaningful or can you assume that if you reduce the amount of sub-straight that it's going to have a clinically meaningful affect?**

A: Not necessarily. Not without some other information I mean if a surrogate marker like that a laboratory test is used for example is used for the basis for approval. We usually like to have it to have a known relationship to some other clinical event like hypertension, lowering blood pressure. You know studies have shown that does have a beneficial affect so in that case we would accept it, for something else a laboratory parameter in an area which we don't really have much experience, to know. That may well be a good thing, but how does it really carry over into something more tangible there we would have more questions about using something like that.

There are some special accelerated approval processes that do rely more on the surrogate marker rather than the clinical end point.

**Q: By clinical end point, do you mean like improvement in respiratory function, or improvement in muscle strength or something like that?**

A: Yes, something that can walk farther, something that sort of on the face of it would be an improvement.



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**Q: So when the company is in there talking with you, do you setup an actual number and say ok you've picked your marker if you can improve that by 20% we will approve, but if you can't improve by 20% we will reject? Or is it kind of more like a negotiation and what you feel like whether it is positive?**

A: Well these can often be difficult questions. We usually challenge the company to provide us with information that says "if this improves by 10% improvement that is something that is really meaningful." For example: in certain respiratory testing, at least for certain conditions or for certain diseases an improvement by 10% is something patients can perceive as being better and if that has been established by some other studies then that would be useful information and to use in trying to decide how big an improvement we've really think to be something important.

**Q: It wouldn't just be for a few select, it would have to be for an average group? Let's say 50% of the group increased by 10% to 20% on the respiratory functions, therefore, that is definitely significant and we will move forward?**

A: Yes, we like to set those ground rules before they go into the major studies so everybody's clear on what the expectations are and to the extent we can, we would like to base it on something other than a good feeling about it. If there is evidence from other sorts of studies, that changes of this kind are really meaningful. That is certainly helpful information, but it can be sort of challenging to come up with something.

**Q: And would you take previous cases from before and look at that data as well, in conjunction with the one year trial we are looking at? Because there is also an expanded access program currently being done right now and would you look at those patients and include them?**

A: Well I am not going to talk about any particular program, but certainly information like I talked about a phase 2 study is where you begin to do some exploratory things to see what the size of the affect of the drug might be and in the context of doing those preliminary studies it well could generate information that will be helpful in setting what the benchmark should be in your pivotal or main studies. It can be a challenge and to some extent its negotiation. We usually sort of put on the company to come back and convince us of whatever targets they are aiming for are going to be meaningful.

**Q: And I have a child that he's 2 1/2 and he started at 8 months, since Pompe they usually die before a year, won't that be a big decision factor too in this particular drug?**

A: We try to adapt to whatever the disease situation that is appropriate for that condition. It is hard to speak in generalities I usually have to get down to the specific cases and that depends on what particular aspect of the disease the drug maybe most affective in treating and that maybe the thing to try to focus on when they do the main studies.



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**Q: Can you talk a little bit about using a placebo and the placebo trial? Initially we were told that wouldn't be necessary and I don't know if you can talk about this, but now it seems like a placebo will be initiated for this next late onset trial. Can you talk about that at all?**

A: Yes, I will get to that in a little bit and I think when I go through the questions we will go through that a little more too.

**Q: Clinically meaningful, do the patients have any role in deciding what is clinically meaningful? Or is it decided by the FDA? Or some other agency?**

A: Well, I mean in some cases well established situations there may be sort of excepted standards on what would be. In cases where we need some new information, certainly experience with patients or patient report and that sort of thing could be helpful in trying to set with the standards maybe.

**Q: I mean if there is a 5% increase in muscle strength or respiratory function. Would you ever consider that not clinically meaningful? I mean is it a statistical significant increase is that always considered to be meaningful.**

A: No, it's not. Often studies are hard enough to do so that often a statistically significant difference will be large enough to be also clinically significant, but a statistically significant change isn't necessarily all we would require of a product in general.

**Q: What if you saw a change a lot faster than what was planned for the one year extension? What if you saw a significant clinical and statistical change within a four month period and even though the trial was set for one year, would you make a move on it then? And change everything and really review and say my gosh we don't need to do this for a full year, let's change it now?**

A: Well, there are certainly a variety of possible designs for pivotal studies. Some of them involve interim looks and some of them are set for a fixed period of time. We'll go and do the study. If there is uncertainty, or a possibility that the effect maybe different or larger, one always hopes better than expected, a study can be designed to actually formally planned to look early with the possibility that we may have more information sooner than we thought and that may be a way to do it, but that usually has to be planned ahead of time because it could be rather difficult then to interpret if it is just something that that cropped up. And things do crop up, and it is hard to really evaluate how unusual that is.

**Q: Doctor, can you please speak later on, what the patients can do if anything in the process?**

A: Ok, I think that some of the questions touched on that too.



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Ok, well then let me continue. We talked about kinds of studies might be done during the IND phase to then get ready for an application. Oh, another thing I want to mention is Fast track, the term fast track sometimes come up, and that is a designation that's given to an IND and what it is, is a recognition by FDA that the product is showing some promise in treating a significant disease where other options don't exist. Then the FDA can designate it as a fast track drug and what that does is guarantees a certain level of accessibility to the FDA during the drug development process. Sort of to the matter of course, we will often meet with the companies they will request meetings with us during the drug development and with good cause. We will usually meet with them and discuss with their program. Certainly a fast track designation makes it much more accessible pretty much any good reason and we'll be happy to discuss things with them and work closely with them if they have that fast track designation also have some implications for how it is treated during the actual application and review later on.

There was a question about who actually does all this work under the IND?

As I mentioned, the FDA isn't really doing it. The company is really responsible for doing these testing. Sometimes smaller companies may actually kind of farm these things out of. There are agencies that are known as (CRO) Contract Research Organizations, which can do some of the animal studies and actually manage some of the clinical studies. Often they are experienced in doing these things so they may be better than some smaller companies. Although, larger companies usually have the personnel and the expertise to run these things themselves, but even the clinical studies they usually are actually done frequently at academic centers and supervised by academic physicians it may not be on the company payroll, but are done under contract with the company.

Sometimes even common diseases the simple treatments may actually be done by large volume specialists out in the community. The company is always the one that is ultimately responsible for making sure the studies are done according to the planned procedures and done correctly. So the studies are actually completed. The company is ready to submit to the FDA for approval sooner to be New Drug Application (NDA), for biologics the nomenclature is a little different (BLA) Biologics License Application, but the procedure is still pretty much the same either way.

What does the company have to provide then, when they come in for approval?

Officially they have to provide information about the manufacturing process of the final marketed product, things like purity and stability and they need to prove they can make it in the sort of volume they are going to marketing it because usually for the IND phase they are talking about small batches, when they want to get approval they are talking much larger volumes. So there are issues of scale up and can they really do the same thing in a large volume and this isn't really trivial. I mean especially for biologic products can sort of be kind of hard to make consistently and so it can be a major issue.

And if you have followed the FDA for a while, you may have noticed occasionally you left something, that a great drug comes along and an advisory committee says yes approve it this is good. Then months pass and six months pass and the FDA doesn't approve it and people say what's



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going on here. What well maybe the problem, is there is a problem with the manufacturing and so that can be one of the sticking points everything else is fine. To really make sure that the factory can do things correctly and the processes are correct. Sometimes that's sort of a major bottleneck and that often something that doesn't get a lot of publicity and that is something that we as the FDA cannot reveal where the issue is. Sometimes the companies aren't necessarily forthcoming as to what the problem is, but that is an important aspect of the approval process.

Another part is the information on animal testing as I mentioned, things like carcinogenicity or reproductive toxicity maybe questions still be best answered with animal studies. So then we would still need to see those and significantly see the results of the major clinical studies and actually we want to see the results of all studies. Basically see any information at all that they have that they know about that is relevant at all to the drug really has to be part of that submission and so it is a very all encompassing requirement.

Now the FDA doesn't just ask for reports, but we really want to see all the data behind them so that means we want to see the datasets, we want to see copies of any report forms that were used, printouts, product test results, and typically we get 10's to 100's literally volumes of information or now it is electronic, but it would be the equivalent of that much information so it is really a large body of information that has to be provided to us.

Now what do we do with it, well is sort of similar to when the IND comes in that we get a product specialist, animal specialist, a statistician assigned to it, a medical doctor or maybe a couple of them, so there will be a small team maybe 3-6 not professional individuals that will be looking through all that information. Typically it will be the people who were working on it while it was under an IND because they are familiar with it already so that is the ideal situation, but sometimes a personnel change or depending on what the particular workload demands are somebody else maybe looking at least at parts of that. Now it is all going to be in the same division and usually with the same team so that similar products everybody is going to know about what's going on. So even if it isn't exactly the same individual that has been working on it during the IND phase there's usually still a lot of familiarity with the product by whoever is reviewing it.

The review timelines the current standards are for a standard type of submission the agency likes to get some sort of response either an approval or what we call a complete response a list of all the deficiencies within 10 months and for something that is a priority review which would usually be a product that had a fast track designation or sometimes others that don't have a fast track designation, but just seem to be turning out particularly well or a significant advance it's a priority review and we like to get a response within 6 months of the submission.

**Q: Do you know if Myozyme is on a fast track at this time doctor?**

A: You know I don't offhand. It seems like it would be a good candidate. I can't be exactly sure. I would have to check the record. We have several products that are.





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**Q: So the sixth month either an approval or the deficiency meaning that you need to get back in and run an additional study or something manufacturing or something like that?**

A: Yes, it's our responsibility to say either yes it is approved or to say no I'm sorry I can't approve it and here are the reasons why and if you address all these reasons then it would be approvable. So we really have to get a complete list of any problems have to be identified by that point of time. We try to be proactive if it is something that is easy enough to fix. We usually try to identify that in the course of the review and give the company an opportunity to fix it. So we just don't sit there silently for six months and then come up with an answer. It's usually active and interactive process so that if there is something that doesn't require a major it's either something they can do differently just for their information that they didn't provide originally, something they can change. We try certainly to work with that so we don't have to go through an additional cycle.

One thing is usually labeling is usually changed in the process of that and there's usually extensive discussion about what the labeling should be so that we can come to an agreement by that time point.

Now the team is really full time reviewers at the FDA, but they've often got other responsibilities too. So it's not going to be the only thing they are thinking about the entire time because they're also usually working on other INDs simultaneously. The reviewers go over the study reports, they see if the data really match what is in the case report forms, we reproduce what is in the statistical analysis, often do additional analysis, really decide which of the conclusions we feel are supported and which ones aren't.

We also have a separate division of scientific investigation. These people actually go out to the study sites, not all of them, but selected sites and do on-site inspections to make sure patients actually existed. You would be amazed what some people try pull even knowing we are looking. It's rare, but occasionally we do find irregularities. So they go out to the sites to make sure that the records were kept properly, make sure that the data that were actually reported to the datasets and the FDA actually match, what's in the patient charts, and lab reports. There are also other inspectors that go out to the factories to make sure that the manufacturing processes is what they say it is and that they were keeping proper records and doing the procedures properly. So in short, these applications are given an order of magnitude of more scrutiny than just say a journal article. Submitted to a journal it is pretty much checked for internal consistency and that's it.

We really go back to the original data we come to an understanding that this study is about as good as you can do just short of actually having done the study ourselves. Sometimes a journal article will come out and everything looks great and the FDA may after looking at all the data actually come to a different conclusion because we have the opportunity to go back to the source. Sort of the end result of all that work is first of all an extensive written report of the findings and that's the reviews produced by the each of product reviewer, the animal study reviewer, the clinical reviewer, and the statistician and eventually if the product is approved these things are usually posted on the web. So that they are available through the freedom of



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information, but usually it is easier now to get it done because of the internet. Certain things though, I mean, it isn't necessarily the complete review because there maybe certain items that are still trade secret information that manufacturing information and occasionally the reviews refer to other unapproved products so that particular part of it won't be there, but usually you get a pretty in-depth picture of what the reviewers thought about it.

**Q: So that is only if there are deficiencies?**

A: No, if it is not approved it won't go out. So it is only if it is approved if it is not approved it remains confidential.