

**South African AIDS Conference 2003
Plenary - Nevirapine
Precious Matsoso: Nevirapine: a Regulator's Perspective
August 6, 2003**

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MODERATOR: -- I think Prudence has spoken for all of us. She has spoken for all the people that we are here to represent because you see, as looking smart you don't actually know that we are not here for ourselves, we are representing concentrates of women who can't come here and say, I buried my child yesterday. And I want to specifically say, after all Prudence has said, I want to salute a young girl who is going to become a young woman one day, she is a nine year old girl called Lucia (Misspelled?). She was looking after her mother everyday she came out of school and I want us all to acknowledge that this is what our children are subjected to until the treatment is available and it makes a difference it has made to Prudence's life. We have to get it. Please.

I'll hand over to the program's Director and thank you very much for the opportunity.

PROGRAM DIRECTOR -- Thank you very much. I'd also like to thank Prudence for sharing her personal experience and pain and frustration on this issue. I'd like to introduce our next speaker, who's Precious Matsoso, who is the Registrar of Medicines at the Medicines Control Council. She is also the Custom Manager of Regulatory Affairs in the Department of Health. She is a pharmacist by training. She trained at UWC and also did a post-graduate diploma in health management at UCT. She is an internationally respected regulator and she has been involved in regulatory issues both locally and

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internationally. This includes the chairing of the Esthetic Harmonization Initiative. She has been on a number of WHO technical committees. She's also on the advisory board of the Global Fund. We welcome her today and we look forward to her clearing up some of the issues surrounding Nevirapine use in South Africa. Welcome.

PRECIOUS MATSOSO: -- Good afternoon ladies and gentlemen. I would like to thank first, Professor Karim for inviting me to speak. I was not on the program to speak today. I was actually on the program to facilitate a session on access to drugs in particular, antiretrovirals, a session that I cultured with Zachie Achmat a day before yesterday. That I did because as a regulator, I register antiretrovirals on a daily basis. I register medicines on a daily basis, but I think what all of you need to know is that when antiretrovirals and any other medicine is registered in this country, it has to meet requirements. Our first priority as a regulatory authority is that medicines must be safe; medicines must work; they must do what they intend it to do; and, their quality must be acceptable and good. For those of you who may not know what the Medicines Control Council is, it's a statutory board that has been established in terms of statute. It has been in existence for more than thirty-five years. And it has been one of the best regulators, within a developing country context, Also as an emitting economy, South Africa has one of the well-

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established regulatory agencies. It has 24 experts from different scientific disciplines, supported by 10 technical aspect communities in the pharmacology, clinical, immunology, virology, various fields, so it's not just a group of people who sit and just decide anything. They make up their minds and they consider whatever decisions they make. The registration of medicines is based on three key principals: quality, efficacy and safety. And the demonstration of quality, efficacy and safety must be substantiated by evidence and I'm here because I'm talking to scientists who understand what evidence is. Mother-to-child transmission remains a problem in developing countries and I think it is for this reason that I agreed to speak today because I think there has been misunderstandings that need to be clarified.

There are a number of interventions that are available. Long and short course antiretroviral interventions have been used. Nevirapine is not the first drug in this country to be used for that intervention, AZT has been in use and there are reports, particularly in the Western Cape of its use. Some of these interventions will be outlined below. Some have achieved regulatory approval and others haven't and MCC has approved, as I speak now, both medicines that are under patent (unintelligible) generic antiretrovirals of those medicines. The interventions that I want to refer to that has been in use for a number of years is the Petra A (Misspelled?) study where

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there is a use of combinations of AZT and (unintelligible) Petra C which has showed efficacy and it's recorded and there is evidence available. We have heard in this conference some of the interventions that are available for use. AZT in combination with Nevirapine that has been referred to. The Malawi study and Thailand (unintelligible) and so forth. Those are available. We've heard in this conference about AZT in combination with (unintelligible), the sample study, I think in Kenya, now that exists. That has been in use and there is evidence for their use. But I think of particular importance what I want to share with you is the experience of the U.S., and people will say what a bad example because it is not a developing country, but remember safety, ethnicity and quality is the same elsewhere as it is in South Africa.

The USA Public Health Service has four options of these interventions and this is a recently published documentation and this is June of 2003. They make recommendation for use of AZT alone, AZT and (unintelligible) in combination, Nevirapine alone, and Nevirapine in combination with AZT. Now for item number 1, 2 and 3, there is no data available to address (unintelligible) but this is what is said in this publication from the US but they have been used in public health programs and these indications are not registered by the FDA, but they are being used in the U.S. Now the problem statement is that, when an application was filed specifically for Nevirapine using

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(unintelligible) 012 the Uganda study was primary evidence in the basis on which approval of Nevirapine was granted, with condition. I think that the consideration of (unintelligible) was that it would be understood that minimal evidence is accepted, but confirming data would be submitted. I think that it is sort of a general principal with most regulatory agencies and I'm sure that with you (unintelligible) we've looked at both. They're used through different regimens. There are letter differences between the two in terms of design and it is for that reason that it could not be (unintelligible) at that point and time because there were problems with same in terms of design but there are certain considerations that are made by a regulatory agency. When we look at data that is sent in to us from clinical trials, randomized clinical trials, (unintelligible) of any intervention for mother-to-child transmission should be demonstrated at different time points with a name to achieve HIV-free survival at 24 months. It's an important end point, which I think all of us should understand and acknowledge. I think of importance is that a regulator does not look at problematic issues of persuading. This is not a regulator issue, but they are considered because they have implications for the achievement of that end point of HIV-free survival at 24 months and it is important that all those issues should be considered. But the history of Nevirapine, in as far as MCC's concern, is that it has been considered in a light of

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considering an intervention they should receive that end point of having babies that are free of HIV AIDS at 24 months and who are also healthy and I think this is the principal. We've received an application, and I want to say that this application was a fast track. Now if you fast track an application, as MCC means you give it priority approval. Priority approval because we considered it MCT was an important issue in this country. But I think in reviewing it we also understood that there was no conformity status and we needed further data. But there was honestly no acknowledgment that there was no data study that was conducted which was (unintelligible) resistance (unintelligible) but also an announcement of it results in (unintelligible).

Now if we sit in a conference like this and someone presents a slide like I'm doing, and announce that there's a new cure for AIDS or there's an intervention. That is not the basis of approval by MCC, you must submit data to us and this is how we work. We need evidence, we need data. But I think the importance of that is that we did get an executive summary from SAINT and that was August 2000 and now we are sitting with an application which we have fast tracked at MCC and we want to confirm it to data because we fast track this priority one to approve, but we only get an executive summary 2000. We go ahead and said okay we can not wait because we want the babies saved (unintelligible) like everybody else, like Prudence and

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(unintelligible). And we take a decision that because we do not want to wait that long, we are going to give this approval based on conditions and then we said the conditions (unintelligible) but we'll also collect some systematical view done by (unintelligible) systematical (unintelligible) view for MCT intervention so we can see if we approve this, with conditions, it's acceptable for the interim. We approved it March 2001 and the final package insert is published in 2001 in April. Now these are the conditions that we said, we said okay because of minimal data that we have, we want six-monthly safety reports from the company. We want any information on local and international use. We want resistance-monitoring conducted. We want a report of efficacy in the event of failure. We also want a report on any known and improper use of Nevirapine in the event it interferes with efficacy and safety. But on the basis of that, we look at SAINT and we say in terms of SAINT, there are no real safety concerns reported in SAINT that is sent to us. Finally the report is sent to us November of 2001 and we also looked at other studies and MCC the statement that I am making is that MCC has considered Nevirapine safe when used for this indication. So-called (unintelligible) stories are not accurate. We are saying that Nevirapine in this form is safe. Now, but we are saying what is the efficacy profile of Nevirapine. We've looked at other interventions already. The efficacy profile of Nevirapine

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(unintelligible) and the basis in which we approved it was 012 of ___ is not acceptable (unintelligible) can also not be used because of problems with design. We have also received expert reports. These expert reports can not substitute clinical data that could have been derived from clinical trends and therefore does not meet regulators requirements. This is a regulatory issue. Now this is consistent with everybody else--what everybody else does. And I'd like to refer to that. MCC and other regulatory agencies, we've looked at various journals, drug information journal published in 1999 that FDA (unintelligible) actually advised regulatory approval and approach to us and to antiretroviral. In the antiretroviral approval process, they had to look at the Phase III clinical data at the time of submission and accept it as conformity data but I think that is needed to be supported by ongoing and conformity data. We spend from between 6 and 12 months (unintelligible) condition and I think this is what we tried to do with (unintelligible) we said we'll approve it with the minimal data we have and then we'll await conformity studies from Boehringer & Ingelheim and we were somehow disappointed. But we did not withdraw, we're still hopeful that there will be more data coming. But we also believed there should be conformity clinical input studies which are sufficiently robust in design to answer questions and yet be sufficiently realistic for patient benefit, meaning in the case of HIV AIDS, we have

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to look at what options there are. Our main objective is to minimize harm and maximum benefit. But also, we have to insure that clinical benefit is demonstrated. In the case of antiretrovirals, there must be achievement of antiretroviral activity that is sustained. It must not just be antiretroviral activity at that point and time, it must be sustained so that people can lead their normal lives. But there are also problematic objectives which may not be (unintelligible) which infrastructure, service delivery, operational effectiveness, provisional treatment and so on. These, MCC does not look into. It is not the duty of (unintelligible) to look at (unintelligible) This is not the duty of the agency. MCC looks at quality, efficacy and safety. There is incorrect perceptions that MCC over-regulates. In some instances, MCC is not as stringent as other agencies and we always wonder which is actually the truth. It may be something in between but what is important with the conduct of clinical trends, and I am appealing to the (unintelligible) and scientists sitting around is that we've got good clinical practice guidelines which are consistent with (unintelligible) JPC guidelines and we've got guidelines for JPC. Now those guidelines are a gold standard for us. (unintelligible) we refer to them and we want to try and comply and met those requirements. What has happened in as far as these guidelines and standards are concerned, we received an application like I said, but that application that

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we received also had a JCP report that said everything is fine, no problems. No actually, there was some problems as a result of a clinical (unintelligible) inspection, but that was later. And we compared all those reports, what was submitted before, what was submitted later, and some of the (unintelligible) and findings that were prepared by Melissa Allen (Misspelled?) of Family Health International. We've compared those and we came to a second conclusion we said okay we're not going to take action and that was last year, more than a year ago, we said we will not take action until we get further information. We communicated with the FDA, we spoke with NIA we met with (unintelligible) and we did all sort of things. And I think what we've been involved in was not an irresponsible action we have been considerably following up on this matter in such a way that it can reach havoc benefits without undermining problems that are already underway. In our communication with NIH, they said that they would go back and look at whether the problems that are identified which were brought to our attention by (unintelligible) and we're were not going to undermine this intervention and when we were informed that that was going to happen, we welcomed it. But when we compared the final (unintelligible) report and what we already had, it was quite clear that there were some JPC violations. There were some discrepancies in what was originally submitted to us and contradictions, and there were problems with all drug

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accountability issues and adherence to clinical trial protocol.

And in terms of this, these are the facts that we have to say:

the accounting for documentation was retrospective. And our

major, major problem is inference, in as far as allocation of

treatment. I think that this is the key problem that we have.

(unintelligible) quality control, adequacy in procedures and

informed consent procedure deficiencies. The (unintelligible)

responded as the Medicine Control Council is that the data that

was requested from the applicant previously was still

considered but we finally went back to say to (unintelligible)

in the event that problems with (unintelligible), can you not

consider an alternative status that can be submitted. We've

been requesting this for months and months and months. And our

problem is that the goal post has been shifted, and shifted and

shifted because we've been sensitive to the programs and we've

been sensitive to the issues and the constitutional

(unintelligible) considered previously.

But our problem is that the response has not been good

and the company has not been forthcoming and we had to be

decisive and in that case we rejected (unintelligible) as a

pivotal study based on all of the work that we had done for

regulatory purposes. The ninety days that we've given to

(unintelligible), is because we could not say we reject

(unintelligible) and therefore as of today you can use

Nevirapine for MCT.

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We've not said that. (unintelligible) Nevirapine today continues to be used for MCT. We have a problem with (unintelligible) we want something that will replace (unintelligible). This is what we want. And in this 90 day period, there must be submission of clinical data for regulatory purpose and I think that this will inform the decision on the outcome and data that is received. We've also looked at what this means. It does not mean that we just make a decision and just said fine, 90 days from day 91 but I think that is what has been said in the media Nevirapine continues to be used for the treatment of HIV AIDS in this country in combinations with other antiretrovirals. We are mindful of the public health response in that the Department of Health has a constitutional obligation to provide Nevirapine or an alternative and we are mindful of that and we will not act irresponsibly. But we also know that there are other programs that cannot be disrupted there are also pregnant women who need to be treated so that their children are not infected. But there are also stakeholders like researchers, like professionals who need to know what need to happen. We are mindful of that. And we've put several options, which is food for thought for you and you need to come back to us as a regulatory authority. In that there are practical interventions that can achieve prevention of HIV transmission from mother-to-child. Different regimens should be

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(unintelligible) for different or greater acceptance.

In South Africa, we need to say which of those regimens should be considered. Experience exists in US, in Botswana, in Kenya, in Thailand where Nevirapine has been used in combination. I've heard in this conference and I've seen other material. And I think MCC needs to see that. But that submission would obviously come from those with interests in this particular manner. It is not the regulator's authority to go around collecting information. There are over 20,000 registered medicines in this country. Now MCC does not do work for any company. Now imagine if we had to go around collecting data for every single product and all 20,000 product, it surely would not make sense. But we are saying combination antiretrovirals are available, there is an opportunity to treat the mother and the baby. But it is not up to the MCC to decide if there is regulatory approval that can be considered. Communication at (unintelligible)interested parties, scientists, departments, service providers, researchers is what we are calling for, to say send whatever submissions, we can meet with researchers if possible, they've requested such a meeting we are willing to meet with them and look at whatever options there are.

In conclusion, Nevirapine is not bent and will not be bent. Nevirapine is important in public health programs for treatment of HIV AIDS and other antiretrovirals. MCC has

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registered a generic Nevirapine and other generic antiretrovirals. To facilitate access but I need to mention that Boehringer & Ingelheim, as an applicant has a regulatory obligation to respond in ninety days. In the ninety-day period, we will sit (unintelligible) programs with researchers and look at what needs to happen from day 91 onwards. Thank you.

[END OF RECORDING]