

1 adulteration, substitution, and hydration, all samples  
2 could be at risk. In here the only samples at risk  
3 are those residing approximately 30 percent above the  
4 cutoff, meaning from two nanograms to 2.6.

5 Now, conclusions. To summarize, in the  
6 application, we have given you five user field studies  
7 that we consider have provided more reliable data from  
8 multiple sources than a single controlled clinical  
9 study may have provided if it were ethical possible.

10 Secondly, the establishment of a dose-  
11 response curve strictly not necessary for an assay  
12 where the decision is are you above the cutoff or are  
13 you below the cutoff.

14 On the pharmacokinetic issues, yes, the  
15 key issue is to detect morphine via the screening  
16 method application to identify heroin users. As with  
17 urine testing dose-response was not required.  
18 Regarding the minimal detectable dose, all the  
19 information that is necessary is contained in the  
20 hair, because it has the ability not only to store, to  
21 trap, but to stabilize over long periods of time.

22 And finally, urine testing for drugs of

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1 abuse did not provide such detailed information as  
2 part of any FDA submission. The ratio and hair color  
3 bias you've heard from Professor Newel. With valid  
4 techniques, meaning the analytical assays in  
5 conjunction with statistical populations, there is no  
6 race or color bias. Statistical treatment and review  
7 of small and large population revealed no evidence, as  
8 you've seen from the previous presenter. There are no  
9 conflicting large population studies in the  
10 literature. The small studies may have conflicting  
11 conclusions that result from different methodologies,  
12 and these are influenced, as we've said, extraction,  
13 efficiency of wash, non-ingestion. And these results  
14 are not unexpected.

15 And, finally, with valid techniques such  
16 as the washing procedure we've outlined, there is no  
17 external contamination issue. In fact, the research  
18 presented in our application has demonstrated that the  
19 exhaustive level of washing effectively removes  
20 externally the positive drug and can ensure with  
21 confidence the differentiation between a heroin user  
22 and a non-user. There are no conflicts in the

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1 literature regarding external contamination provided  
2 the correct techniques are applied.

3 Finally, research models without adequate  
4 washing procedures do not remove contamination.

5 I think that's my last one.

6 Oh, hair treatment. Again, cosmetic  
7 applications, we've seen it can reduce the amount near  
8 the cutoff, and that would only affect three percent  
9 of the samples. And this is a far less effect than  
10 that created by simple hydration of adulteration.

11 And for the last comments, I'm going to  
12 invite Professor Selavka to the podium. We've saved  
13 a little treat for last. Professor Selavka is in fact  
14 co-chair of the Small Working Group for Hair Analysis  
15 under SAMHSA, and he's going to share with you his  
16 views on hair testing and the poppy seed controversy.

17 Professor Selavka.

18 DR. KROLL: Hi. Before we begin, I would  
19 remind you it's about 10:45, which is getting into our  
20 scheduled break, so use your time wisely.

21 DR. SELAVKA: Say again how long I have.  
22 So, I'm between you and food.

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1 (Laughter.)

2 You probably thought I was here just to  
3 run the projector. My name is Karl Selavka. I'm the  
4 Director of the Massachusetts State Police Crime  
5 Laboratory, which has nothing to do with hair drug  
6 testing. So, since you wanted to see somebody  
7 outstanding in their field, there you go.

8 I do have to disclaim I'm not here  
9 representing the state or the executive office or any  
10 laboratories per se. I am hopefully representing some  
11 insight into the operating process of the Hair Testing  
12 Working Group that was sponsored by the Drug Testing  
13 Advisory Board of HHS, as well as poppy seed studiers.  
14 Some day after my wife's vet bills are paid off I hope  
15 to have a conflict of interest. Of course this is the  
16 land of disclaimers.

17 Anyway, I was one of the co-chairs along  
18 with Dr. Donald Kippinberger of the Hair Testing  
19 Working Group to DTAB. We're asked by them to review  
20 the field, and there really are a world of different  
21 samples other than those currently being applied in  
22 workplace testing that could allow for some insight

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1 into a drug use history for a person being tested. Of  
2 those, urine drug testing, sweat, oral fluid, and hair  
3 predominate the matrices that are being studied  
4 currently for applications in the workplace.

5 They all are providing complimentary  
6 information. The complimentariness may be related to  
7 time periods and sensitivity to different substances  
8 and graphically speaking some look into the past, and  
9 one can look into the future. If you were to use all  
10 of the complimentary matrices for each of the  
11 applications in a workplace, a business setting,  
12 forensic examinations, and even post-mortem work,  
13 you'll find that all of them have unique specialties  
14 that they can offer to the particular investigation.

15 But the federal government is now looking  
16 outside the box. They are not feeling that they have  
17 to use a single-matrix approach anymore, and because  
18 of that, they also recognize that the old approach is  
19 the larger approach, and it's going to take some time  
20 to demonstrate adequately to everybody's satisfaction  
21 what needs to be demonstrated.

22 The Hair Testing Working Group was made up

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1 of a number of different kinds of people. Those  
2 actively working in hair drug testing laboratories as  
3 well as interested outside scientists and medical  
4 review officers. A number of federal and non-federal  
5 observers and ghosts and some people that were  
6 providing specific insight into issues since it was  
7 federally funded, we were fueled mostly by doughnuts.  
8 The federal government graciously paid for travel, but  
9 otherwise we were basically on our own. But they did  
10 well for us.

11 We had three meetings, most of which were  
12 attended by volunteers. We put out to the hundreds of  
13 people that have expressed interest in the past about  
14 hair drug testing, a notice that we were going to have  
15 these meetings, an invitations for them to come. We  
16 also had a number of contrarians, people who had  
17 published in contravention to other people in the  
18 field of hair drug testing to try to get their insight  
19 into the process and to try to get their consensus  
20 with us.

21 But after the third of these meetings, I  
22 was invited to also give this to the international

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1 perspective. It's important to recognize that America  
2 is not the only place where hair drug testing occurs.  
3 In fact, in Germany there's routine use, as well as  
4 France.

5 The substances that are listed are those  
6 that are routinely reported in the literature, early  
7 in the literature that comes from those countries.  
8 Canada has presented results in the literature, Japan,  
9 the United States' copious data, and the laboratory  
10 where I used to work, National Medical Services, is  
11 actively involved in esoteric drug and other analyte  
12 testing in hair.

13 This summarizes the drug classes that have  
14 been detected in hair. It's virtually all of them  
15 that can be ingested. But we formed consensus on all  
16 of the components for the most part that we were asked  
17 to by the federal government -- how much hair to  
18 collect, what type of hair to collect, the length to  
19 collect, stability of drugs, collection integrity,  
20 screening cutoffs, which screening precisions and  
21 accuracies were necessary.

22 One of the elements asked us to define the

1 immunoassay cutoffs and what the analytes should be.  
2 Those are listed here for you. We also formed  
3 consensus on the confirmation cutoffs that should be  
4 chosen to limit any claim of external contamination.  
5 These were chosen much higher than the analytical  
6 sensitivities of the assays, but building in factors  
7 recognizing that this particular matrix had not been  
8 used routinely in federal workplace testing, and  
9 therefore we should be overly cautious, using specific  
10 metabolites for amphetamines, opiates, cocaine, and  
11 THC to rule out the presence of external contamination  
12 as the only source of drug being determined.

13 We helped design what we thought would be  
14 adequate blind PT programs and sources for open  
15 quality control materials. The confirmation cutoffs  
16 for opiates are shown here. The difference between  
17 what you've seen the rest of the day and these is that  
18 you have to multiply this times ten, because this is  
19 nanograms per milligram as opposed to nanograms per  
20 ten milligrams. I'm not a mathematician so I always  
21 have to do this for myself.

22 These are the other confirmation cutoffs

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1 in case you care. I know today we're here to talk  
2 about opiates.

3 We were able to reach consensus on  
4 interpretative guidelines, and that is a positive  
5 finding in hair represents chronic and repetitive  
6 exposures and uses during the time period represented  
7 by that hair. It's not a single dose giving rise to  
8 these findings; it's repetitive uses.

9 We talked about what alternative medical  
10 explanations you might have for a heroin-finding hair.  
11 Well, there shouldn't be any. There are no  
12 alternative medical explanations for that. We  
13 discussed dose-response relationships, helped design  
14 what we thought would be a comprehensive PT program,  
15 and for the first time for workplace drug testing  
16 defined what we thought were adequate standards for  
17 tandem mass spectrometry for confirmation.

18 About dose-response relationships, I think  
19 it's important to recognize heroin is an illegal drug,  
20 there's no therapeutic drug monitoring requirement  
21 here. It's sort of counterintuitive to deterrence to  
22 expect there to be a dose-response relationship. In

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1 effect, we haven't held any of the other matrices to  
2 that equivalent standard, and therefore detection is  
3 appropriate, but cautious application of cutoffs is  
4 also appropriate.

5 More consensus. You've heard this well  
6 from Dr. DuPont so I won't repeat it, but bias is a  
7 normal component of all biometric testing. We  
8 recognize that. We also believe that it's important  
9 to have discretion for MROs in order to take into  
10 account different factors of a person's history when  
11 relating drug positive results.

12 Animal models do not generally correlate  
13 well with human use, and low-dose studies should not  
14 be used dispositive of the issue. We know very well  
15 that there's wide differences between the hair on  
16 animals and the hair on humans. Therefore, animal-use  
17 studies have certain application, but they're not  
18 dispositive in any way on the overall studies in the  
19 field.

20 The other reasons I'm here is because I've  
21 done one of the studies on poppy seeds that's been  
22 referred to by some, and also I've recently updated

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1 this and presented at the American Academy of Forensic  
2 Scientists Meeting earlier this year. As part of the  
3 presentation, basically, I'll go over what foods are  
4 out there, the toxicology involved, the fluctuating  
5 policy we've seen, and that there is help.

6 I was the Operations Officer for the  
7 Army's drug testing lab in Hawaii for four years. I  
8 asked for Ft. Meade, Maryland, but they gave me  
9 Hawaii.

10 (Laughter.)

11 In this laboratory, we were at that moment  
12 in time, in the mid-80s, we were bringing opiate  
13 testing on board, and we had to recognize that there  
14 were some issues. One of the issues we got inspected  
15 too often. I did learn the official military  
16 vegetables for urine testing -- leeks and peas. If  
17 you don't get it, I'll explain it later. And you  
18 should never eat anything with the word "whiz" in it.

19 But anyway, opium poppies can give rise  
20 when ingested to morphine findings in urine. There  
21 was some literature at that time, but we recognized  
22 that we might have a problem. We didn't want to

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1 ignore the problem; we wanted to use reasonable  
2 cutoffs in order to define the difference between  
3 poppy seed ingesters and the contributions those might  
4 have to positive findings and those that were using  
5 heroin.

6 When it comes to poppy seeds there's quite  
7 wide variability in worldwide production and the  
8 amounts of opiates that are found in those seeds.  
9 This lists those for you, and you see the word  
10 "thebaine" there. It's one of the opiates that's  
11 found in poppy seeds that at one point was thought to  
12 be maybe that's the magic bullet. We can use thebaine  
13 detection to differentiate poppy seed eaters from  
14 heroin users.

15 There's also wide variability in how much  
16 you eat when you're eating a poppy seed food product.  
17 You don't know whether the seeds were washed or not  
18 washed, the latex on the outside of the seeds may or  
19 may not, depending on the literature you read, contain  
20 the opiates that are in question. You don't know what  
21 the difference might be from cooked and uncooked  
22 foods. The problem is you don't really know where

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1 these things come from when you're eating them.

2 But poppy seeds follow toxicological rules  
3 -- whatever goes in one end comes out the other end.  
4 Those ends could be of course on the top of your head  
5 or various other places. And the concentrations in  
6 urine are generally described here: Less than 4,000  
7 nanograms per mil of morphine, less than 200 nanograms  
8 per mil for codeine, thebaine, generally below 150  
9 nanograms per mil. All in urine and all peaking  
10 around four hours after ingestion.

11 It can be extended if you have a lot of  
12 butter or rum in some of the products that you're  
13 eating. Hopefully you do when you're eating poppy  
14 seeds, because otherwise they're not that delicious.  
15 There is a good deal of high subject intervariability.

16 In order to rule out poppy seeds, in the  
17 late '80s, Mahmood ElSohly and Skip Jones in  
18 Mississippi, described in a paper that there may be a  
19 strategy using toxicologically placed analytical  
20 cutoffs on the confirmation. If morphine was greater  
21 than 5,000, codeine greater than 300, and morphine to  
22 codeine ratio less than two, they described that that

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1 should not be from poppy seed eating. This was  
2 around the time the military laboratory system was  
3 putting in place opiate testing. They also said 6-  
4 acetylmorphine, if you find it, it's heroin.

5 Well, we went in our laboratory. We  
6 wanted to study the effects. We thought, well, if  
7 there's an analytical approach, we may also be able to  
8 join them in the toxicological ingenuity and come up  
9 with this good plan for the military. What we found  
10 is that the reasonable toxicological ingenuity does  
11 not spell good policy.

12 The reason for that is in my own study  
13 with poppy seed ingestion, we found levels of morphine  
14 11,500 nanograms per mil at peak concentration in one  
15 individual; codeine greater than 4,000 nanograms per  
16 mil. The ratios usually work but the cutoffs that  
17 were being applied at 5,000 and 200 were not working.

18 There is very rapid 6-acetylmorphine  
19 clearance. Generally, within three to four hours,  
20 you're not going to have 6-acetylmorphine in urine at  
21 detectable levels. Thebaine is not ubiquitous among  
22 those that eat poppy seeds, and there's always your

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1 idiosyncratic ingester. So, you may have all the  
2 components of a positive, but MROs are routinely not  
3 reporting it as a positive. That's the problem.

4 There have been bouncing cutoffs. The  
5 military, we started with 300 nanograms per mil for  
6 codeine and morphine. We went to 4,000 morphine,  
7 2,000 codeine. It's now back down to 2,000 morphine  
8 and codeine, the Medical Review Office making the  
9 majority of calls in this.

10 HHS' cutoff changes are shown. DOT's  
11 cutoff changes are shown. In their Notice of Proposed  
12 Rulemaking under new part 40, going in for DOT  
13 testing, their cutoffs suggest that at 15,000  
14 nanograms per mil for morphine, there is no  
15 possibility of seeds. It's another hand wasted  
16 toxicological ingenuity. I'm sure we can eat enough  
17 -- if there's enough rum and butter, I'm sure we can  
18 get enough in our body with the right seeds to clear  
19 that 15,000 hurdle. That's not the point. Let's  
20 detect 6-acetylmorphine.

21 Now, taking the pieces apart and designing  
22 a good program, part one is even the federal

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1 government when it was reviewing this issue and  
2 looking at changing cutoffs recognized -- this is Dr.  
3 Autry's testimony in front of subcommittee of the  
4 House in 1998. Essentially, among 1.1 million tests  
5 for drug use, opiate positives at 0.66 percent.  
6 That's 7,294 samples. Eighty-one percent of them were  
7 positive for morphine at a level less than 2,000.

8 So, only 19 percent of the 0.66 percent  
9 had positives greater than 2,000 nanogram per mil  
10 cutoff. And of those, only two percent of the 0.66  
11 percent were positive for 6-acetylmorphine. So,  
12 essentially, if you use 6-acetylmorphine or a cutoff  
13 of 2,000, you're going to miss the predominance of  
14 positives in this population of 1.1 million people who  
15 might be using heroin.

16 But the policy problem is really twofold.  
17 For one point, if labs are doing lots of work and  
18 spending lots of money and time to find morphine-  
19 positive results in urine and MROs are routinely not  
20 reporting them to the company, well, we've wasted a  
21 lot of time and money, and that's not right. So, if  
22 you raise the cutoff, you lower the laboratory burden

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1 and the cost to the system.

2           Unfortunately, higher cutoffs also reduce  
3 your likelihood of deterring heroin use, and that  
4 ultimately is the problem we're after. We're trying  
5 to differentiate poppy seeds from heroin abuse.  
6 Heroin on the street has hydrochloride, or tar heroin,  
7 in a smokable form. We want to distinguish, in  
8 effect, in this model, here's your heroin abuser. You  
9 want to a program that has reasonable detection of  
10 heroin abuse that will build a good deterrence.  
11 Without good detection you don't have deterrence.

12           The other policy consensus that should be  
13 mentioned is cutoffs should reflect drug use while  
14 minimizing potential endogenous, exogenous, and  
15 chemical and electronic interferences. We all  
16 recognize that when you find a piece of a tiger, you  
17 still have to differentiate the tiger.

18           (Laughter.)

19           Another piece of consensus to leave you  
20 with is positive opiate results are conceded by all  
21 toxicologists poppy seeds can lead to positive  
22 urinalysis findings at 300, at 2,000, maybe not at

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1 15,000. You'll find some consensus at levels below  
2 that.

3 So, heroin abuse is definitely increasing.  
4 My crime laboratory continues to receive advancing  
5 numbers of submissions of heroin on a yearly basis.  
6 Poppy seeds creates an evidentiary false positive in  
7 urinalysis; therefore, urine tests are not effective  
8 in approaching the heroin problem. Safety is  
9 compromised, because if you can't detect a heroin  
10 problem, then the safety of the workplace or other  
11 tested population is not good and with basically  
12 elevated cutoffs, lowering deterrence at the very time  
13 that heroin abuse is increasing.

14 When you hear hoofbeats, you think horses.  
15 Well, the good thing is only 6-acetylmorphine proves  
16 heroin ingestion. One piece of bad news is -- or good  
17 news, depending on how you take it -- urine does not  
18 routinely accumulate 6-acetylmorphine in levels that  
19 are detectable, but hair does. Six-acetylmorphine  
20 readily accumulates at detectable levels of hair.  
21 You've seen a lot of demonstration of that in the data  
22 provided today.

1           The last part of this is what the Hair  
2 Testing Working Group provided to DTAB was we  
3 suggested good reporting guidelines and maintaining  
4 MRO discretion in the review of findings from hair.  
5 We believe hair provides the complimentary matrix that  
6 is really needed in the program of deterring heroin  
7 abuse. We should choose unique analytes, like 6-  
8 acetylmorphine, and use the lowest cutoffs we can  
9 while maintaining reasonable safety.

10           This is the information that the  
11 workplace, the employer, and all of us deserve. This  
12 is the information that urine provides. We need to do  
13 a better job, and hair can do that for us. Thinking  
14 outside the box it was nice to know that the Drug  
15 Testing Advisory Board has taken our advice. The  
16 guidelines that will end up in a Notice of Proposed  
17 Rulemaking are under development now. The second  
18 draft is already up; they're working actively on the  
19 third. We're proud to have been a part of that  
20 process. It's a very important time for hair drug  
21 testing and for heroin abuse.

22           I appreciate the opportunity to be here

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1 today. I'll slide out of the way now and let you get  
2 to a break. Thanks very much.

3 DR. CAIRNS: Mr. Chairman, thank you for  
4 the extension of time. That now concludes our formal  
5 presentation.

6 DR. KROLL: All right. Thank you very  
7 much.

8 We're going to take a short break now and  
9 report back to give the FDA presentation in 15  
10 minutes.

11 (Whereupon, the foregoing matter went off  
12 the record at 11:12 a.m. and went back on  
13 the record at 11:26 a.m.)

14 DR. KROLL: If the panel will take their  
15 seats, please.

16 Okay, at this time, we are going to  
17 continue with the FDA presentations. And the next  
18 speaker is Dr. Albert Peacock.

19 DR. PEACOCK: Let me see if I can get some  
20 of your panel back.

21 DR. KROLL: All right.

22 DR. PEACOCK: I didn't want to make a

1 presentation without my Division Director here.

2 Good morning. I'm Al Peacock, a  
3 scientific reviewer in the Chemistry and Toxicology  
4 Branch of the Division of Clinical Laboratory Devices  
5 and a member of the team reviewing this device today.

6 The Psychemedics RIA assay for opiates and  
7 hair that is presented here today is a first-of-a-kind  
8 submission for the FDA for drug abuse testing in hair.  
9 Currently, there are a number of review issues that we  
10 are working with Psychemedics to resolve.

11 Today, I will be presenting to you several  
12 new matrix-related issues that we would like your  
13 input on.

14 I'll summarize for you the study submitted  
15 by Psychemedics that correspond to these new matrix  
16 review issues, and I'll ask you if these studies are  
17 appropriate.

18 This device is a radioimmunoassay intended  
19 for use in the detection of heroin in human hair.  
20 This device produces qualitative as well as semi-  
21 quantitative results for morphine. For a positive  
22 report, two nanograms of morphine per ten milligrams

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1 of hair are required. All positive results must be  
2 confirmed by a more specific method, such as GC, mass  
3 spec, or tandem mass spec or LC/MS/MS.

4 Now, heroin is metabolized in the body,  
5 obviously, to morphine at 6-acetylmorphine, or MAM, 6-  
6 MAM. Consequently, in order to report a positive  
7 heroin result, this device has to identify morphine at  
8 a concentration of two nanograms per ten milligrams of  
9 hair as well as identifying 6-MAM in the mass  
10 spectrometry confirmation.

11 This is an assay flow chart for the  
12 analytical process. There are two pathways that  
13 Psychemedics has presented to us for processing  
14 presumptive positives after the initial digest and RIA  
15 screen.

16 The blue pathway here has an RIA assay who  
17 emits -- get a negative report and the positives go  
18 through the mass spectrometry confirmation. The red  
19 pathway emits the second RIA procedure and goes  
20 directly to the mass spectrometry confirmation. One  
21 of our concerns with this approach is that we don't  
22 think it's been fully demonstrated that these two

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1 assay pathways will produce identical results when  
2 assaying the same sample.

3 A total of 11 field studies were submitted  
4 by Psychemedics. Most of these field studies were  
5 government funded and were designed by independent  
6 scientists not associated with Psychemedics.  
7 Psychemedics was contracted by these independent  
8 scientists to perform hair analysis for their studies.

9 The following study design features are  
10 common to all of the clinical field studies submitted  
11 by Psychemedics. The hair cutoff used was two  
12 nanograms of morphine per ten milligrams of hair. The  
13 urine cutoff for the opiates assay was 300 nanograms  
14 per mil. Of course, you'll note that currently the  
15 opiate cutoff recommended by Sampson is 2,000. And  
16 clinical truth was defined by Psychemedics as self-  
17 reporting in the amount of drug ingested, self-  
18 reporting of the time of ingestion, and verification  
19 of positive drug screen results, urine drug screen  
20 results -- excuse me, I'm sorry, verification by a  
21 positive drug screen, urine drug screen. And these  
22 were not confirmed.

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1           There were two field studies which were  
2 used to determine the minimum detectable dose.  
3 Biofield studies were used to determine clinical  
4 sensitivity or positive percent agreement, one field  
5 study was used to determine the clinical specificity  
6 or negative percent agreement, and three field studies  
7 were used to determine the clinical usefulness of hair  
8 testing.

9           The clinical data from research reports  
10 and data was collected -- other data was collected  
11 from other diverse sources. The self-report and  
12 urinalysis data from these studies were seen by  
13 Psychemedics only upon receiving prepublication copies  
14 of the papers for the final peer review copies of  
15 these papers.

16           We have the following concerns related to  
17 the field studies. These field studies were  
18 uncontrolled, unmonitored, and not validated by  
19 Psychemedics. They had no control of the hair sample  
20 collection process. Psychemedics did not approve any  
21 of the study protocols used. There was no demographic  
22 data submitted for these studies, so we couldn't

1 evaluate or make any kinds of conclusions of the  
2 potential of race, age, sex, hair color or other  
3 individual differences and what their effects could  
4 have been on the results.

5 The field studies lacked the gold standard  
6 method of determining true drug use status.  
7 Therefore, we feel that in place of sensitivity and  
8 specificity, clinical performance should be estimated  
9 in terms of percent agreement with the available or  
10 chosen method of determining drug use status.

11 We also have a concern that the positive  
12 percent agreement has been determined primarily in  
13 clinical studies of heroin users, while the primary  
14 use of this assay will be in a workplace setting.

15 Additionally, self-reporting has several  
16 deficiencies that can influence clinical study  
17 results. These deficiencies include inaccuracy in  
18 remembering amount of drug used and remembering the  
19 time of ingestion, the truthfulness of reporting,  
20 unknown drug purity, varying efficiencies of drug  
21 administrations, such as by injection or by smoking or  
22 by inhalation. Validity of self-reporting may differ

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1 by the drug being used, and the validity of self-  
2 reports of recent drug use may be less at follow-up  
3 than at intake.

4 The environmental studies submitted by  
5 Psychemedics utilized ten hair specimens. The studies  
6 were based on their three-domain properties of hair,  
7 which are the accessible region, semi-accessible  
8 region, and inaccessible domain. Excessive washing,  
9 perming, dyeing, and relaxing hair treatments were  
10 evaluated.

11 The contamination studies consisted of  
12 three separate studies: decontamination of drug pre-  
13 hair specimens that have been surface contaminated  
14 with morphine, decontamination of hair specimens from  
15 heroin users with morphine concentrations above the  
16 cutoff of two nanograms of morphine per ten milligrams  
17 of hair, and potential of contamination of hair --  
18 drug-free hair by simulation of sweating of hair that  
19 has been treated -- surface treated with drug.

20 One of the problems we have in evaluating  
21 this information is there's conflicting evidence in  
22 the literature regarding some of these issues,

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1 especially the potential for bias of testing results  
2 due to hair color. Several human and animal studies  
3 have shown differences in drug accumulation between  
4 pigmented and non-pigmented hair. Other studies have  
5 found that hair pigmentation contributed negligibly to  
6 variations in drug concentration values.

7 However, most studies found in the  
8 literature melanin concentrations in the hair are not  
9 generally determined and correlated to the amount of  
10 drug incorporated in the hair, making the evaluation  
11 of some of these studies very difficult.

12 Psychomedics states that their procedure  
13 spins out the melanin fraction from the dissolved hair  
14 digest. Consequently, any melanin-bound drugs are  
15 excluded from the analytical procedure, and therefore  
16 no hair color bias can be present if the Psychomedic  
17 methodology is used.

18 Now, I'll proceed to the questions. Lunch  
19 is approaching.

20 Okay. Due to the conflicting literature  
21 concerning these new matrix-related issues, we need  
22 input from the panel to help us resolve the following

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1 concerns. Question 1 for the panel: The clinical  
2 data in this application is from research reports and  
3 data collected from diverse sources and not from  
4 perspective controlled clinical trials that evaluate  
5 heroin use. Therefore, a steady hypothesis  
6 inclusion/exclusion criteria associated endpoints and  
7 a plan of statistical analysis were not provided.  
8 First part of this question: Can assay performance be  
9 established with these types of data? Why or why not?

10 DR. PEACOCK: And I'll go ahead and finish  
11 the question: Do the data presented provide adequate  
12 characterization of assay performance?

13 PARTICIPANT: Read them all.

14 DR. PEACOCK: Okay, sorry. Question 2:  
15 With respect to making claims for clinical sensitivity  
16 and specificity, is a single negative urine analysis  
17 plus a negative self-reported drug use a sufficient,  
18 unbiased standard for establishing true drug-free  
19 status?

20 Is a positive urinalysis that is not  
21 confirmed plus a positive self-report of drug use a  
22 sufficient, unbiased standard for establishing true

1 drug-free status?

2 Question 3: Should the minimum dose  
3 required to produce a positive result be determined?

4 Question 4: Should the relationship of  
5 the pharmacokinetics of drug use and the incorporation  
6 of drug into the hair, that is single dose, multiple  
7 dose, and chronic use be determined?

8 Question 5: Should the potential for bias  
9 by race, age, sex, hair color or other individual  
10 differences in the incorporation and retention of drug  
11 in the hair be evaluated? If yes, what additional  
12 studies should be requested?

13 Question 6: Is the information provided  
14 by the sponsor adequate to address the issue of  
15 retention of drug in the hair from environmental  
16 exposure? If not, what additional information should  
17 be requested?

18 Seven, Question 7: Has the sponsor  
19 adequately demonstrated the effects of various washing  
20 or hair treatment procedures on the internally  
21 incorporated bound drug? If not, what additional  
22 studies should be requested?

1 DR. KROLL: All right. Thank you.

2 At this time, I'd like the panel members,  
3 if they have any questions, to ask Dr. Peacock.

4 DR. KURT: Tom Kurt. I'm asking about the  
5 precedence within the FDA of a unique extraction  
6 method, which apparently is unique here -- not the RIA  
7 technique itself, but an extraction method -- and  
8 comparing it to a few years ago when Dr. Ostrea,  
9 that's O-S-T-R-E-A, came to FDA with a unique  
10 extraction method for extracting meconium, or newborn  
11 infant stools, for drugs of abuse in a PMA, and was  
12 that approved, and under what precedence does that set  
13 for this?

14 DR. PEACOCK: I might have to refer to Dr.  
15 Gutman, that was before my time.

16 DR. GUTMAN: There has been -- actually,  
17 I think it was clear -- but there has been a meconium  
18 assay that was cleared, and the precedent is whether  
19 there's reasonable science to support the submission.  
20 It's not anything unique or special. It's a question  
21 of having the right science to make you comfortable  
22 that this works in the way it's intended.

1 DR. EVERETT: James Everett. Is the data  
2 clear as it relates to race and incorporation of drugs  
3 into hair? The sponsors suggest that there is no  
4 difference. Is that true for the literature?

5 DR. PEACOCK: No, it's not. Hold on one  
6 sec. There are several studies that -- Cone, et al.  
7 in 1996 found that cocaine concentrations in hair of  
8 African-American subjects were significantly higher  
9 than those found in Caucasian subjects.

10 Glyxner, in 1996, observed that drug  
11 residues for clenbuterol were lower in light hair,  
12 blond and gray, than dark hair, black or brown.

13 Henderson, in 1998, demonstrated that non-  
14 Caucasian subjects incorporate approximately 2.9 times  
15 more duterated cocaine in their hair than did  
16 Caucasian subjects in equivalent experimental  
17 conditions.

18 Kronstrand, in 1999, observed after a  
19 single oral administration of 100 milligrams of  
20 codeine to non-subjects, the incorporation of codeine  
21 into hair is affected by its melanin content, and that  
22 relationship is exponential.

1           As Psychemedics has mentioned, it's very  
2 difficult sometimes to compare some of this data,  
3 because people use different methods, different  
4 treatment methods, pre-treatment methods before  
5 analysis, and makes comparing some of these results  
6 very difficult. But that's one of the reasons we  
7 brought this question to the panel today to get your  
8 input, because there's such conflicting information  
9 out there from Psychemedics as well as some of the  
10 articles in the literature. We were sort of at an  
11 impasse on what to believe, and that's why we wanted  
12 your input.

13           DR. KROLL: Yes, Dr. Lasky.

14           DR. LASKY: So, based on what you just  
15 said, the uncertainty deals with the drug that was  
16 measured and the extraction technique. Is that a  
17 correct interpretation?

18           DR. PEACOCK: Well, it's the point and  
19 counterpoint. Psychemedics' position is that their  
20 enzymatic digestion process is much better and  
21 especially since they spin the melanin out that they  
22 don't have an issue with this. Whereas some of these

1 solvent extraction processes might lead to a problem.

2 DR. LASKY: All right. So, then that's  
3 really the issue, the fact that in the literature it  
4 says that since that's variable if there is a better  
5 technique, then demonstrate that that technique is  
6 better. And I guess that's the question that in fact  
7 that we're addressing right now, not what's in the  
8 literature but the data that has been submitted,  
9 whether or not that's valid.

10 MS. PINKOS: This is Arleen Pinkos. I'm  
11 also a member on the review team. I think part of our  
12 dilemma is that the studies provided to us did not  
13 have any demographic information associated with it.  
14 So, it was not possible for us to, in an objective  
15 manner, evaluate whether there was a bias or not. And  
16 the information that we do have is the anecdotal from  
17 other people's studies or literature. So, we're just  
18 asking you is the information that is available  
19 adequate?

20 DR. PEACOCK: One of the problems is that  
21 the studies that were submitted to us came to  
22 Psychomedics from their contacts of people doing

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1 studies that were independent of them setting up a  
2 study to answer some of these analytical questions.  
3 And, so some of this demographic information is not  
4 available and will never be available.

5 DR. KURT: Tom Kurt, another question.

6 MS. FLANNERY: A procedural point: Can  
7 Psychomedics address these questions as they come or  
8 are they going to have a chance afterward?

9 DR. KROLL: Right now we're discussing  
10 these things with the FDA panel.

11 MS. FLANNERY: All right. So, they can  
12 address each of these issues afterwards.

13 DR. KROLL: We can allow that. There is  
14 a time for open public hearing scheduled at three  
15 o'clock. We'll provide you some time to go ahead and  
16 try to answer some of the questions. Why don't you  
17 write them down and we can do it in an organized  
18 fashion?

19 DR. CLEMENT: I have a question. You  
20 mentioned the lack of a perspective controlled study  
21 that's appropriately monitored by the Company,  
22 particularly there's no controlled studies of actually

1 ingestion of heroin. That's a real problem. How  
2 would you, in a perfect world, ethically do a study or  
3 how would you envision it be designed to actually look  
4 at some of those issues?

5 DR. PEACOCK: No, I agree with you that it  
6 would be a very difficult study to do, but people are  
7 given morphine and codeine under controlled conditions  
8 all the time in hospital settings. And you could set  
9 up something. People take morphine and codeine under  
10 controlled conditions for pain management and they  
11 take constant chronic doses, and you know what those  
12 doses are. You don't have self-reporting. I mean  
13 those can be administered quantitatively with clinical  
14 drugs as well as monitoring the time.

15 One of the problems we have with some of  
16 these studies is that because Psychomedics did not  
17 design any of these protocols, even though they were  
18 done monitoring people in criminal justice populations  
19 and parole, some of the questions they could have  
20 answered if they had -- if they were going to do it  
21 this way could have been asked but they weren't,  
22 because they didn't have control over the studies.

1 This is data coming to them after the fact, and they  
2 didn't -- yes?

3 DR. CLEMENT: From looking at the results  
4 of the data, they cited four or five studies where the  
5 sensitivity of people that they categorized self-  
6 reported or urine positive testers sensitivities in  
7 the range of like 70 at the low end. It was as high  
8 as 85 percent. I would think if there's an error that  
9 occurred, it would err on the side of less  
10 sensitivity. But from the data that's presented, they  
11 did their own in-house study that showed zero false  
12 positives in their own workers.

13 DR. PEACOCK: Yes. It's not that I'm  
14 arguing with what they did. I'm just asking your  
15 input, because this is the first hair study that's  
16 coming in, and if you're giving the advice that this  
17 is acceptable to you, it will become less of an issue  
18 for us. And we understand that controlled perspective  
19 clinical trials on drugs like heroin, obviously, would  
20 be very problematic. But there are ways to address  
21 some of these issues, we feel, at least for morphine  
22 for sure.

1 DR. CLEMENT: So, if I can rephrase what  
2 you're trying to get an opinion to us what is the  
3 minimum standard acceptable for an approval of this  
4 type of product?

5 DR. GUTMAN: We're actually bringing this  
6 to panel so that you can in fact provide us some  
7 perspective and advice, and I would remind the panel,  
8 since Phil Phillips wasn't here to remind you this  
9 morning, that we are under an obligation to seek a  
10 least burdensome threshold. So, we're not looking to  
11 sell the product short, but we want to do what's  
12 reasonable, and we want to make sure we aren't putting  
13 either incorrect or artificial hurdles up. On the  
14 other hand, we want to have an honest product with  
15 honest performance and honest labeling.

16 DR. PEACOCK: In other words, if you would  
17 agree or you feel comfortable with the fact that a  
18 negative self-report, a negative urine, and a negative  
19 hair test is good enough for a gold standard for a  
20 negative, and a positive urine and a positive self-  
21 report and a positive hair test is good enough gold  
22 standard for a positive, well, that question is

1 answered. But that's why we're asking it, to find out  
2 if you feel that's true.

3 And if you feel that the data submitted to  
4 us from studies that they had no control over, as far  
5 as I know, if data that came in secondarily is good  
6 enough to answer some questions that we feel that  
7 could have been answered with a little more of a  
8 controlled study that they designed versus somebody  
9 else designing. Is that sort of where we're going?

10 DR. CLEMENT: Yes, yes, helpful.

11 DR. KROLL: Dr. Manno.

12 DR. MANNO: Barbara Manno. You said that,  
13 and I read in the materials sent to us, that they are  
14 claiming they spin the melanin out. Have there been  
15 -- is there adequate data comparing one or the other  
16 extraction methods simultaneously against their  
17 procedure?

18 DR. PEACOCK: If there is, I'm not aware  
19 of it.

20 DR. MANNO: What I'm getting at is  
21 melanin-based or lack of melanin specifically, is the  
22 data there for that comparison?

1 DR. PEACOCK: Not that I know of.  
2 Psychomedics might be aware of it. They might be able  
3 to answer that question better than myself.

4 DR. KROLL: Dr. Henderson.

5 DR. HENDERSON: I asked Dr. Newel and  
6 perhaps in the break someone from Psychomedics, along  
7 with Dr. Newel may be able to find some of the  
8 answers. The data that he presented from Glasgow and  
9 London, to use that as indicating that there was no  
10 effect on hair color -- by hair color and hair type,  
11 I think that those are fairly homogenous populations,  
12 and it's unclear what groups were analyzed in those  
13 populations. How were they different? Were their  
14 hair textures, hair colors different?

15 I think there are enough populations that  
16 we are fairly confident regularly used drugs --  
17 incarcerated populations, patients in substance abuse  
18 programs -- where if there was some interest in  
19 looking at whether the test was different in different  
20 populations, that could be done.

21 I'm concerned that the specificities and  
22 negativities are reported in populations that have

1 minimal or -- well, they're identified as admitting to  
2 drug use, and since we're looking at using this in a  
3 general population, I've not seen and I'm unaware of  
4 what the predictive negative and positives are for  
5 general populations that I would assume may have one  
6 and two percent prevalence of substance abuses.

7 So, some of that information I would like  
8 if you could find some of that.

9 DR. KROLL: I wanted to ask a question now  
10 to try to clarify for me and maybe for the rest of the  
11 panel, it appears that Psychomedics has a method  
12 that's pretty inclusive. If someone sends them a  
13 sample, they do the sample preparation that uses RIA  
14 procedure, and then they have a bunch of confirmatory  
15 procedures.

16 Now, what I'd like to clarify for us  
17 exactly what is it that is presented to the FDA for  
18 approval, what portions of that? Because there's like  
19 three major sections, each of which are fairly  
20 extensive.

21 DR. PEACOCK: Right. The submission  
22 itself is for the RIA assay, radioimmunoassay for

1 opiates. But it's sort of like a package. I mean the  
2 up front processing of the hair is critical to the  
3 assay as well as the downstream processing, which is  
4 the washing as well as the mass spec. And especially  
5 for heroin, I mean, you have to see 6-MAM in the mass  
6 spectrometry. So, the application itself for the RIA  
7 assay, but it's such an integrated system that we  
8 can't really exclude any piece.

9 DR. KROLL: All right.

10 DR. GUTMAN: And we would recognize that,  
11 I mean, for most drugs of the assay we would recognize  
12 some reference methodology as an acceptable framework  
13 for reference. So, this isn't -- the matrix is  
14 unusual, but the idea of using a reference method to  
15 try and characterize performance is not.

16 DR. KROLL: That's fine. I mean, I just  
17 wanted to clarify that, because it's a rather -- I  
18 mean there's the whole back-end, which is the  
19 confirmatory portion, isn't really part of the  
20 submission. And it appears like the front end, the  
21 sample preparation, is that part of the submission or  
22 not?

1 DR. PEACOCK: Yes.

2 DR. KROLL: That is part of the  
3 submission, okay.

4 MS. PINKOS: Yes, but the confirmatory --  
5 this is Arleen Pinkos -- the confirmatory method for  
6 a urine test would also not be part of our review  
7 either.

8 DR. KROLL: Right, okay.

9 Okay, and just my intent, what we're going  
10 to do eventually is go through each question, and  
11 everybody speak. So, this is to ask Dr. Peacock. Do  
12 you have any other questions, just to clarify issues  
13 in what he presented?

14 DR. KURT: Were any attempts made to go to  
15 a detox unit in combination with a methadone clinic to  
16 take samples in that kind of a situation where you  
17 actually have patients in that flow path as opposed to  
18 giving them drugs as test subjects?

19 DR. PEACOCK: Psychomedics would have to  
20 answer that question.

21 DR. KROLL: Okay. That's a question we  
22 may actually ask the Company, and what we could

1 probably do is when we come back after lunch is if the  
2 Company can succinctly answer some of the questions as  
3 we get back into the discussion so we can clarify  
4 those issues.

5 Any other questions from the panel?

6 Dr. Manno.

7 DR. MANNO: Manno again. You asked the  
8 question would we be satisfied with a one negative  
9 urine, one negative hair, I believe it was, and a  
10 self-report. Are you talking about hair and urine  
11 collection simultaneously in time or are you  
12 separating them in time?

13 DR. PEACOCK: Psychomedics, their studies  
14 collected urine and I think hair samples  
15 simultaneously.

16 DR. MANNO: Okay.

17 DR. LASKY: Okay. Any other questions  
18 from the Committee for Dr. --

19 MR. REYNOLDS: Stan Reynolds, consumer  
20 rep, and I have just one very simple question: What  
21 is synthetic sweat? I mean is there a standard  
22 formula for this?

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1 DR. PEACOCK: I think you'll have to ask  
2 Psychemedics.

3 DR. KROLL: Okay, Dr. Rosenbloom.

4 DR. ROSENBLOOM: I was a bit confused by  
5 the data that seemed to show that there was a lot of  
6 false negatives among expected drug users. The  
7 percentages were, as indicated, 75 to 90 percent, but  
8 that still leaves a lot of false negatives. And I  
9 wondered maybe that needs to be reviewed by the  
10 Company, those slides, because they're not -- those  
11 tables didn't come through in the published -- in the  
12 handouts. And I'm not sure what that represents.  
13 Maybe you can clarify it and whether if we know how  
14 many RIA negative individuals are subsequently  
15 positive by the GCMS or LCMS testing; in other words,  
16 what the false negativity rate is with just the RIA.  
17 Do we have that data? Did I miss it?

18 DR. PEACOCK: I don't think I have that  
19 data, no.

20 DR. ROSENBLOOM: Well, we need that.

21 DR. KROLL: Dr. Everett?

22 DR. EVERETT: James Everett. The studies

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1 that they used to support the approval of this device,  
2 are the methodologies the same or are they different?

3 DR. PEACOCK: The testing methodologies?  
4 Each individual study was designed independently by --

5 DR. EVERETT: I know they didn't have  
6 control over how they were done, but are the  
7 methodologies the same or are they different?

8 DR. PEACOCK: You mean testing.

9 DR. EVERETT: Right.

10 DR. PEACOCK: As far as I know, they're  
11 the same.

12 DR. EVERETT: Okay.

13 DR. PEACOCK: The testing. And once the  
14 hair sample came in to Psychomedics, they were all  
15 treated identically.

16 DR. EVERETT: But from the different  
17 studies or the different groups that analyzed the hair  
18 samples, initially, are those the same methodologies  
19 or are those different methodologies?

20 DR. PEACOCK: I guess I'm not hearing what  
21 your question is.

22 DR. WILKINS: I might be able to clarify

1 his question for you. I think what Dr. Everett's  
2 referring to is in the published statistical  
3 evaluation that was in the Forensic Science  
4 International 2000 paper that looked at a series of  
5 eight studies that were termed small-scale studies and  
6 that were retrospectively analyzed, the data that were  
7 presented were analyzed and that paper obtained using  
8 the same methodologies employed by the company or by  
9 the sponsor.

10 DR. PEACOCK: I think some of these  
11 statistical studies were done on existing Psychomedics  
12 data. They were pulled out of the Psychomedics  
13 database is my understanding. Like I say, it's not  
14 totally clear to us either, so maybe Psychomedics can  
15 give us a little clearer answer on that.

16 It's my understanding, when I was reading  
17 I think the same article you were, is that it's sort  
18 of like Psychomedics has a database of hair sample  
19 results, and then --

20 DR. EVERETT: But these are secondary data  
21 sets, right?

22 DR. PEACOCK: Say it again.

1 DR. EVERETT: These are secondary data  
2 sets.

3 DR. PEACOCK: Yes.

4 DR. HENDERSON: May I just ask one  
5 question?

6 DR. KROLL: Yes.

7 DR. HENDERSON: Is the FDA aware of any  
8 false positives that have been reported for heroin  
9 using this methodology?

10 DR. PEACOCK: I'm not, no.

11 DR. KROLL: Okay. Does the panel have any  
12 other questions for Dr. Peacock?

13 DR. WILKINS: I do have one more, and I  
14 may have missed it in the material, so I apologize if  
15 I did. But has the sponsor proposed a monitoring  
16 program or a follow-up to track reports of either --  
17 or inconsistencies between perhaps what the MRO might  
18 perceive to be this is a drug user, and I keep getting  
19 negative results or this is someone who will never in  
20 a million years I would have predicted to be positive,  
21 and yet I'm getting positive hair tests. Is there  
22 some type of monitoring proposed to kind of assess for

1 that once it were to be introduced?

2 MS. PINKOS: We have not discussed that  
3 with the -- this is Arleen Pinkos -- we have not  
4 discussed that with the sponsor, but that certainly is  
5 something you can give us input on.

6 DR. LASKY: Can I --

7 DR. KROLL: Yes, Dr. Lasky.

8 DR. LASKY: Fred Lasky. I'd like to  
9 comment on that. Presuming that this device will be  
10 cleared for market, the device is subject to quality  
11 system regulations, good manufacturing practices.  
12 Part of that requirement is to monitor all complaints  
13 and to address all complaints and investigate what the  
14 source of those complaints -- what the source is. So,  
15 your question is a requirement once a medical device  
16 hits the market. I'm a little surprised that this  
17 device, which will be used only within this laboratory  
18 is in fact going through this process, but that's the  
19 sponsor's option.

20 And I think also, based on Dr. Kroll's  
21 question that I think is part of what I'm having also  
22 some difficulty in segmenting but the clarification

1 was helpful, in that we're looking at a collection  
2 device, which has not really been questioned from what  
3 I've heard or seen in any of the data. An internal  
4 RIA method that in every case will be confirmed with  
5 an accepted, definitive method. And to me that seems  
6 like almost like the device is the whole package, and  
7 the reference method, the confirmatory test, I guess,  
8 has met other standards that everybody is comfortable  
9 with.

10 So, from my standpoint, the only real  
11 question is not the presumptive positives of the RIA  
12 tests, because they will be verified by the definitive  
13 method, but the potential for a false negative and how  
14 that might be addressed and whether or not the data  
15 support that. That's what I'm waiting to get some  
16 clarify on.

17 I had the mike, so I just went on and on.  
18 I'm sorry.

19 (Laughter.)

20 DR. KROLL: Any other questions from the  
21 panel?

22 Okay, it's about 12 o'clock now. What I'd

1 like to do is we'll take a break for lunch. We'll  
2 come back exactly at one o'clock. At that time, I  
3 think Psychemedics has written down some of the  
4 questions that the panel had. We'll give them ten  
5 minutes to try to clarify those issues, and then the  
6 panel will go in and start trying to address each  
7 question.

8 We'll adjourn till then.

9 (Whereupon, the foregoing matter went off  
10 the record at 12:06 p.m. and went back on  
11 the record at 1:07 p.m.)

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## A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:07 p.m.)

DR. KROLL: I'd like the rest of the panel members to take their seats, please.

All right. I'd like to resume after lunch.

And now I believe Psychemedics was going to answer some of the questions that were queried before and any other additional questions that the panel may have. And what we can do is we go and discuss the questions. If other issues arise, we then can -- we'll ask Psychemedics to clarify those issues as they occur.

DR. CAIRNS: Thank you, Mr. Chairman.

Ten minutes, or whatever time we've been allotted, is a little short, so we're going to try and make our answers as scientifically brief as possible.

Let's deal with the studies that were submitted, in other words, the clinical studies from the methadone or heroin user clinics. We find that more appropriate than trying to use a hospital study with critically ill people just on morphine sulfate.

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1 The ingestion of heroin is a different issue from in  
2 fact the deliberate giving of morphine sulfate to a  
3 chronically ill patient. So, we would reject that  
4 suggestion.

5 However, let me emphasize that the five  
6 studies, A through E, that were presented to you all  
7 used the same RIA assay method as is being applied for  
8 approval. And we use the same hair test and the same  
9 cutoffs. So, in essence, the five studies, while  
10 independent of Psychomedics, used all the same  
11 methodology.

12 Secondly, there is demographic data, and  
13 I'm sorry the panel member who asked the question is  
14 absent, but if you look at some of the attachments  
15 where in fact the results of studies A through E were  
16 published, you will demographic information on  
17 ethnicity, race, gender, color. Those are all  
18 embedded in those publications.

19 The next thing that came up, basically,  
20 was the issue of bias. And you heard me say in my  
21 presentation there are no conflicting studies. It's  
22 the issue of using different methodologies. But let

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1 me turn this over for a more succinct analysis by  
2 Professor Newel.

3 MR. NEWEL: Thank you. First of all, I'd  
4 just like to reiterate a couple of major points.  
5 First, on all of the large-n studies that we looked  
6 at, there were no -- there was no evidence of any  
7 conflict between them. We all had the same results.  
8 And what's important in the large-n studies is that  
9 with the exceptions of the data from Glasgow and Las  
10 Vegas were basically run under different  
11 methodologies. All the other studies, the large-n  
12 studies, were run under the Psychemedics methodology.  
13 That's actually a plus, because what we've seen as  
14 independent evaluators in this issue is that we can't  
15 find any bias even with other methodologies used.

16 In regards to the small-n studies, Dr.  
17 Peacock referred to a number of them as saying that  
18 there seemed to be some conflict in the literature,  
19 and actually referred to most of the studies that I  
20 originally showed. I'm glad that he did that, because  
21 this allows me to emphasize an important point.

22 First of all, none of those small-n

1 studies used the Psychemedics methodology. All of  
2 these original authors only showed mean  
3 concentrations. In one study, they had three African-  
4 Americans, and they reported a mean concentration for  
5 African-Americans and for the four or five, I can't  
6 remember, Caucasians.

7 Well, it would be nice if the world were  
8 as simple as simply looking at the averages of two  
9 small means like that and being able to draw a  
10 conclusion that would have any validity in a  
11 population. It would be nice. As Dr. Peacock  
12 correctly pointed out, one author actually did use the  
13 word "significant." He said that there is a  
14 significant difference in African-American  
15 populations.

16 Unfortunately, that was probably a misuse  
17 of the term. What we're concerned with is statistical  
18 significance. And, so small-n studies simply don't  
19 have the statistical power to be able to show those  
20 kinds of differences when we ran the appropriate and  
21 standard statistical test on their data, on the data  
22 that was originally published by all the same authors

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1 that Dr. Peacock referred to. None of those studies  
2 showed statistical significance except for the  
3 Kronstrand study.

4 The Kronstrand study had nine people.  
5 When we look carefully at that data with a linear  
6 regression, one data point is considered an outlier.  
7 In other words, one person seemed to throw the results  
8 into a significant result. Now, we can't say at this  
9 moment whether or not that's an indicator that there  
10 is a problem with codeine or not. I think it's too  
11 early. But remember it's based on nine people and one  
12 person in particular that had an extreme score.

13 Finally, make a comment about the racial  
14 diversity in some of the papers that we talked about.  
15 I mentioned very briefly a paper by Ben Hoffman that  
16 appeared in Journal of Clinical Occupational Medicine,  
17 I believe. It's a recent paper; he had 1,800 people.  
18 And I gave the reference to the one member who hasn't  
19 joined us yet over the break. That had a very large  
20 and diverse population. It was a group of police  
21 officers. So, it was workplace testing. It was not  
22 a user population. Drug use was found in only a small

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1 percentage of these people, yet again he found no  
2 significant hair color, race or ethnic bias.

3 And also I want to point out that of all  
4 the studies that we reported you have copies, I  
5 believe, in the journals that you have. And our  
6 experiences with this have included criminal justice  
7 populations, probationers, and arrestee populations.  
8 I spent a lot of time in jail cutting hair. A very  
9 ethnic and racial diverse group. So, we certainly  
10 have a lot of diversity in our data.

11 I think that's it.

12 DR. CAIRNS: Thank you, Richard.

13 We've heard some panel questions  
14 concerning false negatives, and I'd like to turn this  
15 over for a compare and contrast of the false negative  
16 issue, urine versus hair.

17 Dr. Selavka.

18 DR. SELAVKA: Thank you. I'd like to say  
19 for the record I was never in prison cutting hair.

20 (Laughter.)

21 I think on the issue of false negative it  
22 requires review of the nature of determining the true

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1 value of use history for a person who's having their  
2 hair collected. There's been no question, and the  
3 question was actually posed and answered correctly, of  
4 a false positive with hair testing. Hair tests  
5 accurately identify heroin users. They have for 13  
6 years with this particular sponsor. Frankly, there  
7 are many other laboratories that routinely detect the  
8 presence of 6-mono acetylmorphine and morphine in the  
9 hair of heroin users.

10 The predictive value for the test  
11 therefore demonstrates that you'll have a  
12 significantly higher positive rate among tested  
13 individuals for heroin when you use hair compared to  
14 urine -- eight percent versus 0.6 percent in one of  
15 the tables that's provided for you.

16 If you were to turn this question on its  
17 head and say that if the question for false negatives  
18 was let's use the gold standard of self-reported use  
19 of heroin and a positive hair test, urine would have  
20 a very low analytical sensitivity, because the false  
21 negative rate is so high.

22 So, I think if we do look at the

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1 clinically significant, the procedurally significant,  
2 and the programmatic significant question, which is  
3 false negatives, you actually have a much better  
4 program with hair than you would with urine. I think  
5 we need to remember that.

6 If you add to that the fact that there's  
7 a medical review officer at the receiving point of a  
8 laboratory's output and that they're routinely not  
9 going to forward or verify those results from a urine  
10 test to a company, therefore no action will be taken  
11 on a positive, on the other hand you'll have a much  
12 more effective and far greater safety measure with  
13 hair testing for opiate positives, because MROs will  
14 forward hair positive results.

15 So, I wanted to put the false negatives  
16 into context that way. Thank you.

17 DR. KROLL: All right, thank you.

18 Any other questions from the panel, from  
19 the group right now? We can ask some questions later  
20 on too.

21 Dr. Lasky?

22 DR. WILKINS: Can I ask a question?

1 DR. KROLL: Well, Dr. Lasky is first.

2 DR. WILKINS: Oh, I'm sorry, Dr. Lasky.

3 DR. LASKY: Okay. I have a general  
4 question about your history with the use of this  
5 particular test. And as we discussed earlier, there  
6 were issues about the complaints in handling and how  
7 you resolve them. And with 13 years experience, can  
8 you just summarize for us any issues that you have  
9 received from people who use your facilities and how  
10 you've resolved them with regard, of course, to the  
11 accuracy of the tests?

12 MR. THISTLE: Regarding heroin-positive  
13 results, in 13 years of testing, with several million  
14 samples being submitted, I had looked for an opiate or  
15 a heroin claim that I could have showed you when I  
16 showed you the cases when I was speaking. I couldn't  
17 find any court cases on heroin.

18 I looked back to see if we had claims in  
19 that regard, and I couldn't find any until I was  
20 reminded that we do have one in several million tests  
21 of a high user that's claiming as part of a union  
22 issue, first of all, the right of the company to test

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1 but also challenging his result. And, so I have one  
2 claim in several million tests.

3 DR. KROLL: Okay. Dr. Wilkins?

4 DR. WILKINS: Yes. I have just one other  
5 question. And I guess I may have missed this, and I  
6 want to make sure I understand. But is the intent of  
7 the submission to determine heroin use only, because  
8 that's what I keep hearing for determining heroin  
9 users, heroine users, and -- let me finish my  
10 question.

11 The reason I ask that is because reading  
12 through the documents that I have, which may not be  
13 perhaps everything that's necessarily been submitted,  
14 it appears that the product would be used for "opiates  
15 in general" is how it's termed. And, so therefore  
16 morphine due to codeine ingestion, morphine due to  
17 morphine ingestion, morphine due to heroin ingestion.

18 And I just want to make sure that I  
19 clearly understand the intent that you -- the setting  
20 or the specific application you want to use it for,  
21 just so that I comment later appropriately. Thanks.

22 MR. THISTLE: The intended use has been

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1 narrowed to opiates due to heroin use.

2 DR. WILKINS: Okay. So, it's only heroin  
3 use.

4 DR. KROLL: Dr. Manno?

5 DR. MANNO: Could we go back to the  
6 negative bias again? I just want to ask a simple  
7 question: Is it safe for me to make the conclusion  
8 that the bias in the negative direction -- let me  
9 state that again -- the bias is towards the negative  
10 side when it comes to hair color? The less hair color  
11 the more chance you're going to have of having a  
12 negative.

13 MR. THISTLE: I'm not sure I can answer  
14 that.

15 DR. MANNO: I think what I'm doing is  
16 trying to look at the other side of the coin. I'm  
17 thinking if you have a very blonde person, a White  
18 person, you'd have less of a chance with a low  
19 concentration of picking up a negative or more of a  
20 chance of getting a negative than a positive.

21 DR. CAIRNS: I think the bottom line  
22 answer is there is no bias, first of all, even on the

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1 negative side, because, remember, the melanin is spun  
2 out of the assay for the confirmation step.

3 DR. MANNO: Okay.

4 DR. CAIRNS: And for the RIA step.

5 DR. MANNO: Did you present studies in  
6 here, I may have missed them, where at some point to  
7 show the difference between having the melanin present  
8 and the melanin absent?

9 MR. THISTLE: Yes. As part of the studies  
10 that were submitted, there were results from  
11 Psychomedics where the melanin is spun out, but there  
12 were also evaluations of laboratories that don't do  
13 that. And you're not seeing statistically significant  
14 deviations in any of those studies.

15 DR. MANNO: Okay.

16 DR. WILKINS: I'm going to ask another  
17 one, just because it's following up on the same issue.  
18 Can I do that or should we wait and come around?

19 DR. KROLL: Well, Dr. Clement wondered if  
20 he could ask one.

21 DR. WILKINS: Okay, go ahead.

22 DR. CLEMENT: Well, I can defer to that.

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1 DR. WILKINS: Okay. We'll bounce back and  
2 forth.

3 The one question I have and perhaps -- and  
4 I'm not a statistician, so I'm going to refer this one  
5 just for the statisticians in the room. But when you  
6 do a retrospective examination of literature, peer-  
7 reviewed literature to support a particular hypothesis  
8 or to test a specific statistical hypothesis, it seems  
9 to me that there are several really important things  
10 that you need to look at.

11 One is which you've already pointed out,  
12 the small size of the studies, is whether or not these  
13 studies have adequate numbers of subjects. Well, you  
14 can't have it both ways. Either they have too small  
15 of a subject to be able to rely on the data and use it  
16 or it does. So, it seems to me like if these are very  
17 small studies and have low statistical power, they  
18 couldn't have determined a difference anyway.

19 So, they were not capable of answering  
20 that question, plus were the studies originally  
21 designed to look at that issue? And I think  
22 restricting it only to the opiate papers, not to

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1 cocaine, not to MDMA, not to MDE or any other assay,  
2 because to me, just as a reviewer, those, in my mind,  
3 are not pertinent to your application per se, because  
4 you want to do this for opiates. So, I'm going to  
5 restrict it just to the opiates.

6 And if you go back and look at those  
7 studies that were not originally designed to do that,  
8 the population that was selected for the two studies  
9 in particular weren't selected for this purpose. So,  
10 I don't know if additional -- there may be some  
11 additional variables coupled with a low sample size  
12 that we don't even know. So, relying on two negative  
13 studies seems to me be as doubtful or inclusive as the  
14 one or two human subject, controlled dose subjects  
15 that are.

16 So, for example, the other -- one more  
17 issue, is that, again for the statisticians, if you go  
18 back and retrospectively examine data that was not  
19 originally designed to look at this question at all,  
20 does not use the same analytical techniques -- one of  
21 the two papers I'm referring to just was a methanol  
22 wash, I wouldn't expect it to agree with your data

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1 anyway -- and then do a one-way ANOVA only looking at  
2 hair color and a single time point, I might not expect  
3 to see a difference either.

4 I mean I'm not -- as I say, I'm not a  
5 statistician. If you had that data and you were doing  
6 a multiway ANOVA with dose, for example, or age or  
7 hair color or gender, whatever, it doesn't really  
8 matter to me what the issue was. But it seems like  
9 you sort of need to control for that in some way,  
10 whether it's analysis of covariance if you're looking  
11 at dose and hair color or something.

12 And I'm just trying to understand how you  
13 can use it to support the fact that there's no hair  
14 color bias if you don't know all those things. And  
15 maybe I'm too simplistic, and that's a statistician  
16 question. I just don't know.

17 MR. NEWEL: I would agree with you,  
18 everything that you've said. I think one of the third  
19 or fourth slides that I had up said why is this likely  
20 that we see four of the five studies when we reanalyze  
21 these data using appropriate statistical techniques?  
22 Why do those initial --

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1 DR. WILKINS: Is that for codeine studies  
2 or opiate studies? I'm just referring to just the  
3 opiate studies, because I'm trying to define. I don't  
4 want to confuse the issue in my mind, because you  
5 haven't asked me to look at cocaine.

6 MR. NEWEL: Okay. With whatever studies  
7 we reviewed there the essential points were that these  
8 are small-n studies. They do not have the sufficient  
9 statistical power to be able to show us that there are  
10 or are not racial bias issues.

11 The point that I was trying to make is to  
12 draw your attention to the fact that the original  
13 authors on papers that said there may be some relation  
14 to melanin content or hair and drug incorporation,  
15 those original authors did not use statistics. What  
16 they said was, "Here's a big mean, here's a little  
17 smaller mean, and therefore, maybe, who knows, there's  
18 some relationship." What we do is take their same  
19 data --

20 DR. WILKINS: So, those two opiate  
21 publications did that? I wasn't aware that that's  
22 what they were trying to say. My understanding was is

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1 the first one was used to evaluate a method  
2 development. And the second one was to develop  
3 whether or not you could even detect heroin and that  
4 kind of a thing in hair, which is a different  
5 question. That's why I'm asking it.

6 MR. NEWEL: Right.

7 DR. WILKINS: I want to really understand  
8 this.

9 MR. NEWEL: That's the second part of the  
10 question, is how do you go back and use what are  
11 basically secondary data analysis for these issues?  
12 Because in some cases, even with the large-n studies,  
13 we don't have the original authors. On some of the  
14 articles, like the Glasgow study, were never intended  
15 to collect data for the purpose of comparing hair  
16 color or melanin content and drug concentrations.  
17 That just happened to be in their data set. We became  
18 aware of that and utilized that data on a secondary  
19 data analysis.

20 Now, that's not an illegitimate  
21 statistical technique. It's done -- secondary data  
22 analysis is done all the time. That is not the

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1 associated with their A priority hypothesis testing at  
2 all. We're basically using an existing data set and  
3 reanalyzing it, not with any particular hypothesis  
4 test in mind, other than to say is there some  
5 association between these two variables?

6 DR. WILKINS: Okay.

7 DR. CAIRNS: In some cases, I believe it's  
8 a mischaracterization of a piece of research work that  
9 was put together to answer an entirely different  
10 question. So, I think the data we presented is we've  
11 got one Psychemedics opiate, statistically valid  
12 study. The others really ought to be removed from the  
13 table, because they don't even measure up to it as  
14 regards. And the study design originally intended to  
15 address the issue whereas the other studies are  
16 mischaracterized as conflicting but small-n and other  
17 experimental difficulties.

18 MR. THISTLE: Some of the studies that  
19 were provided to you on other drugs were actually  
20 provided because you were given studies originally on  
21 other drugs. We would agree that perhaps a cocaine  
22 study has no relevance here, and if you were to not --

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1 DR. WILKINS: I didn't mean to imply that.  
2 I just meant I was trying to narrowly focus my  
3 examination to not bring up irrelevant issues. I  
4 didn't mean to imply that it wasn't good to have  
5 looked at that material.

6 MR. THISTLE: But I agree. For the  
7 purposes of this application, for looking at an opiate  
8 assay submitted by Psychomedics, the important studies  
9 would be the results obtained by Psychomedics with  
10 their opiate assay and not necessarily the results  
11 obtained by someone else with another methodology for  
12 another drug. And that's what I think you should be  
13 focusing on.

14 DR. KROLL: Okay. Other questions?

15 Dr. Clement?

16 DR. CLEMENT: I have one question. I  
17 guess it's more of a comment on one the slides on the  
18 assay performance for the clinical specificity on the  
19 handouts we have. It's on page 8. This is regarding  
20 panel question 1. It was also on the Powerpoint  
21 presentation as well. Would you like to comment? Did  
22 you actually mean to put results true positives or is

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1 that -- I mean --

2 DR. CAIRNS: Is this the slide saying,  
3 effectiveness of urine versus -- of hair versus urine?

4 DR. CLEMENT: No, no. This is the  
5 clinical specificity test that was done on the in-  
6 house employees. N equals 81 --

7 DR. CAIRNS: Oh, yes, I have it now.

8 DR. CLEMENT: You had at least written on  
9 here, and you may want to look at it, it says the  
10 results are true positives for N equal 81s. Does that  
11 mean all your patients were positive for heroin use?

12 DR. CAIRNS: No, no. I'm sure we meant  
13 that they were all negative. I apologize.

14 DR. CLEMENT: Okay. I just wanted to  
15 verify that. That would be very happy employment.

16 DR. SELAVKA: This wasn't PCP. This was  
17 a --

18 DR. CLEMENT: Okay. I just wanted to  
19 clarify that. So, if we swap those, the correct  
20 numbers -- those true negatives were 81; false  
21 positives were zero. Is that correct?

22 DR. CAIRNS: That's correct.

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1 DR. CLEMENT: And then your formula  
2 obviously is correct. So, your specificity is 100  
3 percent.

4 DR. CAIRNS: That's correct, sir.

5 DR. CLEMENT: Thank you.

6 DR. KROLL: Dr. Rosenbloom, did you have  
7 a question?

8 DR. ROSENBLOOM: Well, I'm back to my  
9 confusion about negatives. Do we know how many in  
10 those who you expect to have -- those who are in  
11 treatment programs and so forth, how many negatives  
12 are obtained in that population and how many negatives  
13 in the RIA are retested and found positives in the  
14 definitive test? Does that make sense?

15 DR. CAIRNS: I think you're asking the  
16 question is were all of the positives via the RIA  
17 morphine assay, were they confirmed as positive heroin  
18 users?

19 DR. ROSENBLOOM: Yes.

20 DR. CAIRNS: The answer would be yes.

21 DR. ROSENBLOOM: Okay. So, there would be  
22 then no reason to look for false negatives in the RIA.

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1 DR. CAIRNS: The cutoff level is  
2 determined so, a, the poppy seed ingestion is not  
3 detected as a false positive.

4 DR. ROSENBLOOM: Right.

5 DR. CAIRNS: So, the cutoff is a  
6 protection mechanism so that the poppy syndrome does  
7 not enter into the equation in the determination of  
8 false positives. The two nanogram cutoff is still  
9 there to be able to detect a minimal detectable dose  
10 of 173 milligrams per month, which is very little  
11 concern with the consumption of the average heroin  
12 addict on a monthly basis.

13 DR. KROLL: Dr. Kurt has a question.

14 DR. KURT: Dr. Cairns, I'd still like to  
15 clarify, because you've explained to us how in  
16 separate scientific articles the extraction method has  
17 shown so many results as positive. And then in other  
18 articles not using the extraction methods there are so  
19 many positives. If you'd explain to me in the same  
20 scientific article that samples were divided, some  
21 were extracted and some weren't, were the same number  
22 of positives above the two nanogram level received or

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1 is the extractor group fewer than past the two  
2 nanogram bar for positive?

3 DR. CAIRNS: Yes. Let me go back to a  
4 fundamental procedure again. That first RIA sample is  
5 an unwashed sample. The second sample, should it be  
6 presumptive positive, is washed. So, the question  
7 came up was the comparison of the two different flow  
8 charts within the lab. And, yes, we've done  
9 comparisons. They're in the submission, volume 3,  
10 page 1 through 23. And there was no significant  
11 results between the two mechanisms.

12 DR. KROLL: Okay. Thank you. Are there  
13 any other questions before we proceed to try to answer  
14 the questions.

15 Okay, Dr. Everett?

16 DR. EVERETT: Most of my questions have  
17 been answered, but I'm still unsure about the issue of  
18 the FDA indicating that the literature says one thing  
19 and then you guys are saying something different; that  
20 is, whether or not the literature supports the  
21 differences between the biases where you say there is  
22 no difference, and race is only one of those. In your

1 opinion, is it the same or is it different?

2 MR. THISTLE: The differences don't exist  
3 in the large population studies regarding bias. And  
4 the differences don't exist in any study utilizing the  
5 technology that we're putting forward here. There's  
6 no study that utilizes this technology that is in  
7 conflict at all.

8 With regards to the other issue of  
9 external contamination, there is no conflict in the  
10 studies. We do a wash of three hours and 45 minutes  
11 and analytically extend it another five hours. Some  
12 of the literature that you have has a wash mechanism  
13 of 30 seconds. There's no conflict there. We know  
14 the 30-second wash will not remove external  
15 contamination if it's present. That's not a conflict,  
16 that's just the differentiation in procedures.

17 DR. EVERETT: Then you're sure that when  
18 you say it's removing contamination from the external  
19 surface it truly isn't leaching from the internal  
20 surface.

21 DR. CAIRNS: Yes, I think we demonstrated  
22 that on the wash profile for a typical heroin user

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1 where you saw the third, fourth, and fifth wash  
2 approach a plateau value. So, you could imagine the  
3 external being removed and then reaching a plateau.  
4 If you continued to wash, that would diminish,  
5 diminish, diminish, and then suddenly you have this 30  
6 nanograms of morphine as a skyscraper against the  
7 profile of the wash. So, there's a clear way visually  
8 to distinguish a user from someone who's  
9 environmentally contaminated.

10 DR. EVERETT: Well, the reason I mention  
11 that, because in perm and bleaching hairs, frequently  
12 there is damage. And in looking at the studies as  
13 retrospective studies, as a prospective study, that  
14 doesn't seem to bear out.

15 DR. CAIRNS: Yes. Obviously, when we  
16 quoted to you that certain cosmetic treatments would  
17 in fact reduce the levels, that is because some of the  
18 outer regions of the hair are in fact structurally  
19 affected. But please remember that what goes in  
20 easily comes back out easily on the wash kinetic  
21 profile that we use. So, there's the level playing  
22 field. What goes in easily comes back out easily if

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1 in fact you're dealing with treated hair.

2 DR. EVERETT: It doesn't appear the  
3 playing field is really level, because the  
4 retrospective studies were not -- many of them, as I  
5 look at them, weren't designed to do that.

6 MR. THISTLE: I know what you're saying.

7 DR. EVERETT: But the data is presented by  
8 using that fashion, but they really were never set out  
9 to do that.

10 MR. THISTLE: I know what you're saying,  
11 but the element of consistency between studies A  
12 through E and the large population studies that were  
13 deliberately designed to look at biases, there's a  
14 consistency thread in the methodology running through  
15 these. So, you can do direct comparisons. Our  
16 problem is comparisons where methodologies such as 30-  
17 second wash with methanol, that is no way can be  
18 compared to a result from an extensive wash procedures  
19 that's previously demonstrated to show the  
20 differentiation. You must first of all differentiate  
21 external from ingested before you make any statements  
22 as regards bias.

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1 DR. KROLL: Can I suggest we continue now?  
2 We can try to clarify these issues as we proceed.

3 DR. EVERETT: I have one other question,  
4 and that deals with the essence of deciding to do this  
5 as a retrospective study, and I think many of these  
6 questions could have been most appropriately addressed  
7 as a prospective study. I'm interested in your reason  
8 for choosing retrospective data as opposed to  
9 prospective data.

10 MR. THISTLE: The contamination studies  
11 that -- the question I think started out with  
12 contamination issues and leaching of drug out of hair.  
13 The contamination studies weren't done with  
14 retrospective data. We submitted data on hair that we  
15 contaminated.

16 And I think we're confusing two different  
17 issues here. The retrospective data was done for the  
18 sensitivity and specificity. And there's some  
19 retrospective data on studies that look at hair color  
20 and race and denoted those features. And I'm not sure  
21 what the difference between -- those features don't  
22 really change, whether you're looking at the data

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1 retrospectively or prospectively. Those are standard  
2 features that you can look at regardless of when you  
3 get that data.

4 But I think we're mixing two things.  
5 We're mixing contamination studies with -- actually,  
6 I think we're mixing three things here. We're mixing  
7 contamination with bias studies, which were separate  
8 from the retrospective, clinical  
9 sensitivity/specificity studies.

10 DR. KROLL: Okay. Why don't we proceed  
11 now, and thank you very much.

12 DR. CAIRNS: Thank you, Dr. Kroll.

13 DR. KROLL: Does Dr. Peacock want to come  
14 back up and ask the first question for us? Is he  
15 here?

16 DR. PEACOCK: Can I just make one  
17 statement before we put the questions up?

18 One of the reasons we're here today asking  
19 these questions is for the very reason you're asking  
20 the questions of Psychomedics. The literature is  
21 conflicted, and we had trouble deciding what is  
22 correct and what is not. Psychomedics has their

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1 position. People in literature have different  
2 positions with different methods, and that's one of  
3 the reasons we're asking these questions of you today,  
4 to help us get a feel from the experts that aren't  
5 directly involved in the review.

6 I'm just supposed to read the questions  
7 now.

8 (Laughter.)

9 Sorry.

10 Question 1: The clinical data in this  
11 application is from research reports and data  
12 collected from diverse sources and not from  
13 perspective controlled clinical trials that evaluated  
14 heroin. Therefore a study hypothesis,  
15 inclusion/exclusion criteria, associated end points,  
16 and a plan of statistical analysis were not provided.

17 A, can assay performance be established  
18 with these types of data? Why or why not? And, b, do  
19 the data presented provide adequate characterization  
20 of assay performance?

21 DR. KROLL: Okay. What I'd like to do is  
22 start with Dr. Everett, and then we'll work our way

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1 around counterclockwise.

2 DR. EVERETT: Okay. For question 1, can  
3 the assay performance be established with these types  
4 of data? Certainly they can, but the question would  
5 be whether they were reliable or not, and I don't  
6 think they really would be reliable considering the  
7 data that we've already looked at.

8 And then the second part: Do the data  
9 presented provide adequate characterization of the  
10 assay performance? Clearly not, and that's because  
11 the intent in the studies are different than what I've  
12 seen at this point. So, I just tend to disagree with  
13 this.

14 DR. WILKINS: I agree with Dr. Everett's  
15 comments, and I think for me I do agree that in some  
16 cases, again, that certainly this type of data  
17 analysis can be very useful and helpful. However, I  
18 think that especially for a new or first-time  
19 application or first time it's been seen, we don't  
20 have a lot to compare to, to go on. That unless we've  
21 controlled for some other -- for some critical  
22 factors, and I'm not necessarily intimating that means

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1 hair color, for example, or anything like that, but  
2 unless the study is, in my mind, adequately controlled  
3 for those potential variables that might have impacted  
4 on the quantitative data that's being used to support  
5 the application, I just don't feel like it's  
6 sufficient to go and try and pull that out  
7 retrospectively from someone else's data in some  
8 cases.

9 The reason I think that's important is not  
10 so much related to the specific techniques used but  
11 rather to the package insert and interpretive  
12 guidelines that are going to be provided for the  
13 consumer. And for me that's the bottom line in my  
14 mind is do the studies that are incorporated to make  
15 the particular points, are they adequate to support  
16 whatever we're going to tell the consumer for  
17 interpretation. And I do not feel comfortable in  
18 doing that unless the study has additional controls.  
19 And right now I don't feel that that's there.

20 DR. KURT: Tom Kurt. As a Medical  
21 Toxicologist, I would like to say that I'm quite  
22 enthusiastic about the prospects of hair testing

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1 versus the problematic existence of easy cheating that  
2 has arisen under the urine drug testing. However, I  
3 cannot say that my enthusiasm buoys me over the  
4 problematic issues that both Dr. Everett and Dr.  
5 Wilkins have explained, with which I agree.

6 DR. KROLL: Martin Kroll. I tend to be in  
7 agreement with what previously has been said. I mean  
8 I tend to see that retrospective studies can be used  
9 if they all are basically in agreement and they sort  
10 of cover most of the possibilities. And from the data  
11 I've seen submitted I'm not seeing that here. It's  
12 not there, and it can't be collected, but it's not  
13 necessarily apparent that it's all here. Even a small  
14 prospective study with very clear hypotheses and set  
15 goals perhaps can clarify some of the issues. I think  
16 the fact that so many people here on the panel are  
17 confused about what information is presented and where  
18 things stand points out one of the problems.

19 There's also other issues that we keep  
20 coming back to hair and hair color. I guess I get  
21 concerned with hair treatments. There's a lot of  
22 variation. Certainly, there could be some small

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1 studies there where you take an equivalent amount of  
2 hair and treat it many different ways so that you can  
3 look at all the many different types of treatments.  
4 I think those are things that at least I feel are real  
5 important for the FDA to consider. And I would like  
6 to see that in a submission.

7 DR. MANNO: I can't add anything more to  
8 what's already been said. I agree with all that's  
9 come before.

10 DR. LEWIS: Sherwood Lewis. I, likewise,  
11 am in agreement with the foregone statements by the  
12 panel.

13 DR. CLEMENT: Steve Clement. Well, I  
14 never have troubles disagreeing with my colleagues on  
15 some issues, and I think on this one, looking at the  
16 practical issues of prospectively doing a prospective  
17 study of challenging folks with heroin, which is the  
18 actual agent to be analyzed, is very problematic, not  
19 only in this country but anywhere in the world in  
20 terms of inducing tolerance, inducing addicts,  
21 inducing all kinds of dependency. The studies are  
22 never going to get done.

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1           And the sponsor did submit these four or  
2 five studies that did user assay. Actually, I think  
3 there's some benefit of not having the sponsor  
4 involved in the data analysis, because clearly that  
5 alleviates some of the bias that could be done in-  
6 house by the sponsor, and the studies were pretty  
7 uniform.

8           So, I think even though it's imperfect  
9 data in terms of looking at sensitivity, it's the best  
10 there is, and I don't think I could come up with any  
11 recommendations to improve on that based on the  
12 difficulties of treating this disease.

13           And the issues on specificity look like we  
14 cleared up. It looked like most of the employees are  
15 very happy but not on drugs, so it makes it 100  
16 percent specific, which is fine with me.

17           DR. HENDERSON: Well, I actually gave my  
18 comments earlier, I think, inappropriately. I  
19 certainly agree that there's problems with  
20 retrospective data. But I too agree that I don't  
21 quite know how else you could do that. But I do think  
22 that there are opportunities to obtain retrospective

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1 data or perhaps even prospective data in diverse  
2 populations.

3 I mean the data that we were submitted  
4 from the studies I think without seeing the  
5 demographics, because I gather that's not available,  
6 but just from the location of the studies, I think  
7 they're probably fairly homogenous populations, and  
8 that concerns me.

9 Again, I think most all of these were in  
10 populations that were known to use substances  
11 illicitly, and some of my concern in the workplace is  
12 what are the predicted values for groups of people who  
13 do not have a history of using substances?

14 DR. ROSENBLOOM: Yes. I agree that it  
15 would be nice to have populations defined  
16 prospectively and with the ability to answer all these  
17 questions without rejecting the retrospective data,  
18 which is convincing. But I think that there are more  
19 studies that need to be done. So, I guess I'm halfway  
20 between what's been said by everybody else.

21 DR. KROLL: Okay, thank you, Dr.  
22 Rosenbloom.

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1 DR. LASKY: Fred Lasky. First, I think  
2 that the small studies should just be dismissed, and  
3 I think that was the intent of the presentation; that  
4 they're not statistically valid, no conclusions can be  
5 brought from them, so we should just forget about  
6 them. We should consider the larger studies that were  
7 done to demonstrate the effectiveness or  
8 ineffectiveness of the method that's under  
9 consideration. And I think that's what we need to  
10 concentrate on.

11 I think that retrospective data is okay,  
12 but you have to be very careful with it. So, I  
13 wouldn't dismiss the fact that this is retrospective  
14 data. And it also brings to light the fact that  
15 there's over a dozen years of experience that has been  
16 had with this assay and the fact that hair testing is  
17 based on what we've heard earlier in the day is really  
18 an important matrix to look at.

19 And with that in mind, I think there are  
20 two issues, at least, that I'm trying to pull apart in  
21 my mind. One is, is hair as good as people who are  
22 using the test believe it is? And I think that's one

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1 of the issues that is in question. But I think that  
2 is true regardless of which test is being done. So,  
3 I don't think that the test -- that the submission  
4 before us is in a position to either answer that  
5 question one way or another if it's going to be an  
6 accepted practice.

7 I believe that the sponsor has done  
8 studies that demonstrate in reasonable studies that in  
9 fact hair is a reasonable matrix, that they've done  
10 adequate studies to demonstrate that they've taken the  
11 precaution to exclude as much as possible any  
12 contamination that may occur from the outside. The  
13 washing steps I think are -- and the data are  
14 convincing in my mind. And the way they handle those  
15 data demonstrate to me that they are making an effort  
16 to reduce the possibility of a false positive.

17 So, I think if there is an issue to be had  
18 here it's whether or not the sample that is collected  
19 provides useful information with all of the steps that  
20 is in the submission. And I believe that the sponsor  
21 has demonstrated that the sample mix and based on  
22 what's in the literature demonstrates hair is a

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1 reasonably effective sample, and that they do a good  
2 job in trying to measure what's actually ingested  
3 through hair analysis. So, I think it's reasonably  
4 convincing.

5 MR. REYNOLDS: Stan Reynolds. I agree  
6 with the point that Dr. Clement made that there's  
7 really no way you're going to set up a controlled,  
8 clinical study for hair. You're just not going to do  
9 that. But at the same time, as Dr. Henderson and some  
10 others pointed out, that doesn't preclude the  
11 possibility of gathering the demographic information  
12 that you want.

13 I mean there's no reason that you can't go  
14 to methadone clinics and treatment groups and get  
15 samples from people who are known heroin addicts and  
16 at the same time have all the demographic information  
17 that you need: race, age, ethnicity, hair type. All  
18 that information would be available.

19 So, at the same time, you can design a  
20 study that would give you all the demographic  
21 information to have and have the confirmation of the  
22 standard urine test, confirmation by GC/mass spec or

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1 anything else that you need to show a positive is a  
2 positive and a negative is a negative, at the same  
3 time getting all the demographic data.

4 And we just don't have the demographic  
5 data here. You know, we're comparing apples and  
6 oranges. You have study done one way, one study done  
7 another way. I believe the data that they have  
8 presented for the test is compelling. It shows that  
9 the test does work. But we don't know about the  
10 population demographics. That's just the information  
11 we don't have at this point.

12 DR. KROLL: All right. Thank you.

13 Why don't we go now to question 2.

14 DR. PEACOCK: Question 2: With respect to  
15 making claims for clinical sensitivity and  
16 specificity, is a single negative urinalysis plus a  
17 negative self-report of drug use a sufficient,  
18 unbiased standard for the establishment -- for  
19 establishing true drug-free status?

20 And part B: Is a positive urinalysis that  
21 is not confirmed plus a positive self-report of drug  
22 use a sufficient, unbiased standard for establishing

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1 true drug-free status?

2 DR. KROLL: All right, thank you. And  
3 this time we'll start with Dr. Clement, and we'll work  
4 around clockwise.

5 DR. CLEMENT: The first question, I think  
6 it may be the best we have, a single urine analysis,  
7 although we know the inherent problems with that. And  
8 particularly with self-reporting, there's incredible  
9 problems with that. It's not the gold standard, but  
10 it's the best we have. But I think in this case it's  
11 really not applicable, because in the data that was  
12 presented by the company it was 100 percent negative,  
13 and they're showing not only data of a single  
14 urinalysis but multiple urinalyses as well in a fairly  
15 contained population. I think that's probably the  
16 best that can be potentially done in any type of  
17 situation.

18 So, I think it may not be the best  
19 standard, but it's probably the best that we can ever  
20 hope for.

21 And on the second question, I was trying  
22 to think in my own mind why would someone self-report

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1 positive taking drugs for some other reason besides  
2 he's really taking drugs, unless it's to try to get  
3 room and board in some rehab center, and he's not  
4 taking drugs.

5 So, clearly, there could be some  
6 underestimation on that. But even if that's the case,  
7 that would underestimate the performance of the assay  
8 as opposed to overestimating the performance of the  
9 assay. And in the numbers that are shown here, the  
10 performance is in the range of 70 to 80 to 90 percent.  
11 So, even given that problem, if anything, because it  
12 would potentially underestimate the performance, it's  
13 still not bad at numbers of 80, 85 percent.

14 So, I say, yes, it's probably true, but  
15 it's probably too true and unrelated in this case.

16 DR. KROLL: Dr. Lewis.

17 DR. LEWIS: I'm of the school with regard  
18 to A and B, which says you don't believe anything you  
19 hear and only half of what you see. And as far as  
20 self-reporting, I put it in that first category of  
21 what is it you hear from the individual as far as  
22 claiming use or non-use. So, I have to sort of reject

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1 both of those on that basis.

2 DR. MANNO: Manno. I'm a little bit with  
3 Dr. Lewis in terms of dependability of self-reporting.  
4 My experience has been that the percentage of people  
5 that are honest in these situations is not too great,  
6 so I have a problem there.

7 But, again, we don't have too much more to  
8 go on here. So, I guess a negative urinalysis and a  
9 self-report if you're going to be able to do -- and  
10 I'm taking this to mean in the -- at the end of the  
11 overall scheme of things to make an interpretation  
12 that you may perhaps see this person back later. I  
13 guess I can go along kind of tentatively with A.

14 I've never been one to rest easy not  
15 confirming a positive urinalysis, so I'm not too  
16 comfortable with that. I would much rather see it  
17 linked up with a hair sample confirmation, but then  
18 again there's a problem with when is it going to be  
19 seen in the hair. We haven't even discussed that here  
20 today. What is the delay from use to the first time  
21 you can detect it in hair? So, I'm just uncomfortable  
22 with both A and B, as the way it's presented. I'll

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1 just leave it at that.

2 DR. KROLL: Martin Kroll. I tend to agree  
3 with Dr. Manno. I'm looking at this, and from the  
4 data that was presented a single negative urinalysis  
5 will a lot of times -- there could be a lot of false  
6 negatives there. So, I think you probably need  
7 something a little bit more than that to establish a  
8 negative.

9 DR. KURT: Tom Kurt. A single negative  
10 urinalysis is too easy, as we know, to cheat on  
11 nowadays, and so it's not necessarily a reliable test,  
12 but that's what we rely upon under the DOT standards.  
13 Nonetheless, we know the self-reported histories are  
14 totally unreliable, and I'll cite the Australia study,  
15 the same Australia that I referred to earlier in  
16 pediatrics in 1993 who studied the meconium stools of  
17 3,000 infants in Detroit and found that 44 percent of  
18 them were positives for opiates, cocaine or marijuana,  
19 and questioned the same mothers and found that 11  
20 percent, or one out of four, of the mothers admitted  
21 they were using drugs of abuse during pregnancy. So,  
22 one out of four admitted.

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1 A similar Fendrich study reported in the  
2 American Journal of Epidemiology last year on 320  
3 samples of hair found only one out of our told the  
4 truth about their drug abuse that was verified by hair  
5 sampling.

6 So, self-reported history is generally  
7 markedly underestimates or is reasonably wrong. And  
8 it's much more reasonably under two, or B. The B  
9 portion is if the positive urinalysis is reviewed by  
10 a reliable medical review officer in questioning the  
11 person to find out whether or not they've been using  
12 other drugs that could possibly render a test positive  
13 under the circumstances.

14 I would say that a secondary sample, such  
15 as the hair sampling test once it becomes more  
16 accepted into the Department of Transportation review,  
17 should be acceptable in a medical review officer's  
18 situation also. But I can't rely upon the self-  
19 reported history. I reliable upon a reliable  
20 laboratory test.

21 DR. WILKINS: This is Dr. Wilkins again.  
22 I just want to comment. I don't have anything in

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1 addition to add to the previous speakers. I agree  
2 with actually aspects of all of the previous comments.  
3 And my significant reservation is the issue of relying  
4 on self-report and the issue of a single urinalysis  
5 result coupled with the timing issue of collection.  
6 And I'm not -- I'm using that simply for -- the study  
7 design is where I'm concerned about that. So, that's  
8 it.

9 DR. EVERETT: James Everett. My concern  
10 here is that the initial test is considered to be a  
11 screening test. It's not a guarantee that you're  
12 going to be drug-free. But given the limits of  
13 science and the sociological impacts, part A where it  
14 indicates that the negative urinalysis plus a negative  
15 report is okay with me. That part is okay. You can't  
16 retest everything.

17 But when you develop a positive test at  
18 this point, the general rules for screening tests is  
19 to select out those people who most likely have what  
20 you're looking for, and they are cheaper, they're  
21 easier to perform, and the idea is that you will  
22 follow-up on a positive screening test to determine if

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1 it is a true positive or if it's a false positive.

2 So, in reality, performing a screening  
3 test without some method for determining if it's truly  
4 positive is almost irresponsible. It's like why would  
5 you screen somebody for a disease and then you find  
6 the disease on a screening test but you don't look to  
7 make sure that it's there. So, it's not reasonable to  
8 perform this test, then get a positive test, and then  
9 rely on the person's report now to determine if you're  
10 going to do the confirmatory test.

11 The rules have to be consistent with any  
12 scientific test. If this is how you're going to do  
13 it, then it can't be based on what the person says.  
14 It has to be based on the results of the screening  
15 test, not necessarily the report of the person,  
16 because if you do, it opens up again this ram for  
17 abuse where perhaps the screening test was tampered  
18 with. And now you induce a false situation where a  
19 person admits to something they really weren't doing  
20 or they did but it wasn't in that time frame.

21 So, in reality, you must be consistent  
22 with the rules. If the screening is positive, then

1 the confirmatory test must be done regardless of what  
2 the person's history.

3 MR. REYNOLDS: Stan Reynolds. And I  
4 pretty much agree with everything the folks in the  
5 Committee have already said. I don't have any  
6 additional comments.

7 DR. LASKY: Fred Lasky. I'm not  
8 completely comfortable with the use of these methods,  
9 but as Dr. Clement mentioned, I don't know what else  
10 to do, quite frankly.

11 I have two comments with regard to what  
12 other people have said and also just an editorial  
13 note, that many years ago, probably about 15 years  
14 ago, Ray Gambino reported in his lab report to  
15 physicians that he had done a study, actually he was  
16 looking at sensitivity of lab methods for alcoholism,  
17 and he determined that in fact a self-report was more  
18 sensitive than a serum alcohol level for determining  
19 alcoholism. And it seemed to me, that was quite  
20 enlightening for me as a laboratorian, that just  
21 asking a patient would provide more information than  
22 I could provide from the laboratory was a tremendous

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1 blow to my ego.

2 But it seems that these sort of patients  
3 or subjects would not want to self-report unless there  
4 was -- I would think there would be bias to say that  
5 they weren't drug users and they were. And the intent  
6 of these samples is to provide a challenge to the  
7 method that's being evaluated to have a high  
8 probability that indeed these samples did have drugs  
9 in them and that that is the only reason that these  
10 samples were selected.

11 If in fact the subject did lie, it seems  
12 to me that that would be a greater challenge to the  
13 method that is being evaluated because of the reliance  
14 of being truthful on this, quote, unquote, "gold  
15 standard" as tarnished as it is.

16 So, my bottom line assessment is it's far  
17 from perfect, but I don't know how else to do this.

18 DR. ROSENBLOOM: Rosenbloom. Yes, I have  
19 with looking at either A or B as a gold standard,  
20 because we're talking about evaluating a test that is  
21 measuring something quite different than what a urine  
22 test measures. And we're talking about true drug-free

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1 status if looking at B a positive urinalysis not  
2 confirmed, that's not confirmed on a repeat urine I  
3 take it, not on the same urine -- on the same urine,  
4 okay. But a positive self-report could relate to drug  
5 use in the past but not in the past few days and why  
6 that would establish a true drug-free status I can't  
7 imagine. So, I have trouble with these, because I  
8 have trouble with the concept of a gold standard for  
9 sensitivity and specificity for a test that could be  
10 itself the gold standard that's replacing or saying  
11 something else about drug-free status. But I don't  
12 like either A or B. I guess that's what I'm saying.

13 DR. HENDERSON: Well, I certainly, as  
14 others have mentioned, and there are problems with  
15 both of those, but having taken care of a lot of  
16 pregnant drug users in my special population, I think  
17 the self-reporting is a good edition, although new  
18 mothers may not confess to having used drugs that  
19 their babies are obviously suffering the exposure.  
20 But certainly pregnant women are very likely to admit  
21 it primarily because they're afraid that not admitting  
22 it will jeopardize the health of their fetus. So, I

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1 tend to believe women when they tell me that.

2 So, it may just be a special population,  
3 but I don't really have objections to either of these,  
4 although obviously they're not perfect.

5 DR. ROSENBLOOM: I think we have to be  
6 careful about interpreting admission data for alcohol  
7 as people will readily admit that they've had a few  
8 drinks, particularly if they know that they're going  
9 to be tested, and they know the reliability of the  
10 testing, and it's a legal drug. So, people will admit  
11 to smoking too, but I don't think that relates at all  
12 to illegal drug use.

13 DR. KROLL: Okay. Good. Thank you.

14 Why don't we proceed and go to question 3.

15 DR. PEACOCK: Question 3: Should the  
16 minimum does required to produce a positive result be  
17 determined?

18 DR. KROLL: Thank you. And this time I'd  
19 like to start with Dr. Wilkins, and we'll go  
20 counterclockwise.

21 DR. WILKINS: Thank you. I think my  
22 answer to this is truthfully it depends in that if the

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