

Update from FDA
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DR. WINN-DEEN: I'd like to introduce our two speakers from FDA. I don't know who is up first here on the schedule.

DR. GUTMAN: I'm first.

DR. WINN-DEEN: So Steve Gutman, who we know and love from his many years of service to SACGT and this committee, is going to give us an update first on the diagnostic side of the pharmacogenomics pipeline.

DR. GUTMAN: Yes, good morning. Dr. Rudman and I are going to play team tag here. So I'll start and he'll finish.

I guess my remarks to a certain extent will both support and belie the notion that there's nothing new under the sun. FDA and my work in particular has brought to market in the last year the first two I think what you could characterize as pharmacogenomic tests. The first was approved in December of last year, and that is the Roche Amplichip, and the second was approved over the summer, that is a UGT 1A1.

There were common themes in the review process for both of those products. Those products were brought through as Class 2 medical devices under a new de novo classification that was created for metabolic enzymes. The de novo process is a process that provides FDA with increased flexibility when it encounters a new test of this type, a lack of clear predicates, it does require either low risk or some ability to mitigate risk.

FDA's assessment was actually somewhat parallel for both of these devices, in that what makes these products stand out as tests is their analytical strength and their clinical imperfections. Their clinical imperfections being rather transparent.

Both of these submissions were preceded by changes in CDER drug labeling for at least a model product. In the case of the Roche, that model product was Strattera. In the case of UGT 1A1, the model product was Irinotecan. The labeling changes that were made on the model product were advisory or cautionary, not strong required labeling changes. So they were modest changes, but they were changes on which we were able to feel comfortable about anchoring the de novo clearance process.

In all honesty, we do understand that the clearance of both products based on those models is a little bit like the Titanic approach the iceberg, that we looked at the tip, and there may be a little bit more than meets the eye.

Certainly if there were specific claims and specific performance parameters that were to be generated on top of either of these assays, we would probably like to be revisited with more submissions. That would probably be okay for UGT 1A1 since it doesn't seem to be an infinite spectrum of possibilities.

That might be more problematic for the Roche Amplichip since about 20 percent of medications in the country theoretically could be impacted. We could have dosing decisions, perhaps even selection decisions driven by information generated by the Amplichip, and that would provide incredible job security if we were to go after 20 percent of U.S. medications.

The medications that were best credentialed probably now, but certainly at the time of clearance were the neuropsychiatric drugs, and certainly the use for toxicity seemed very straightforward.

But as Emily sort of alluded to, there are some outstanding education use and reimbursement issues that FDA did not resolve when it cleared these two products. We were good for our word, in that when we talked at SACGT about dealing with these new tests, we said we put these tests out trying to be as transparent as possible to let people know what we knew about the test, and to follow Elliott's admonition, to also be sure that we communicated what we didn't know about the test.

More globally, as Emily alluded to, there is a very novel from our work ethic point of view, a concept paper which represents a joint effort of the Center for Drugs, the Center for Biologics, and the Center for Devices on the co-development of diagnostics as they might relate to drugs.

It is a long document, maybe it's a little too long a document, but in my view, and I'm bias because I'm close to the document, it rather reasonably limns in a preliminary manner the scientific issues on the plate for analytical validation of this type of test, for clinical validation of this type of test, and for elucidating the clinical utility for this type of test.

It makes a very important point that when a diagnostic is used to select a drug, the two become inextricably intertwined, and that I think most people are cognizant of the fact that the diagnostic may drive the performance of the drug. I think a more arcane and missed point is that the performance of the drug may drive the performance of the diagnostic, because the response to the drug behaves for the diagnostic in the same way that prevalence behaves for diagnostic, and can radically change the prevalence of a response, and therefore can radically change the predictive value of a positive and negative result.

That is very parochial and arcane, but a very important point. It is hidden in Appendix C of this concept paper. Anyone who actually is interested in that should look at Appendix C, because we actually tried to make that simple.

The comments, and we did get wonderful comments, a wide range of comments, but probably the most powerful two comments were the comment that the document, which was certainly not intended to be prescriptive and suggest that one size fits all, but was clearly aimed at an idealized development pattern, that it wasn't flexible enough, or it didn't recognize the need for flexibility, and didn't perhaps recognize in a strong enough manner the need for addressing the non-congruence between the life cycle of drugs and diagnostics.

I think that that wasn't the intent of the document, but that's the way the document read, and that's something that does need to be addressed. The work plan is to take the concept paper, which is really quite a preliminary scientific document, and convert it into draft guidance. That would allow for a second round of comments, and then the draft guidance would become final guidance.

I won't promise this time course because we missed the last one by a couple of months, but there was at least the intent. We will try and get the draft guidance out by the end of this calendar year.

There is also some specific guidance, actually the guidance of Dr. Mansfield, who is sitting to my left, originally worked on when we were lucky enough to have her, which started as sort of a multiplex document, and now is more focused on genetic and pharmacogenetic tests. That document is more specific, certainly more diagnostic specific, and is in the final stages of review. I, again, don't promise it will come out this year, but I hope it will come out this year.

SACGHS Meeting Transcript
October 19-20, 2005

We continue to explore changes in guidance and changes in regs to clarify what is still a rather messy area. Actually about two weeks ago, and I want to thank Carolyn Jones who is also in the audience, AdvaMed actually submitted a frequently asked questions document that for us, and probably for them as well, was somewhat unprecedented in that the document and frankly private entities both in the trade sector and in the professional sector frequently provide us free advice and offer us guidance documents which we will sometimes laugh at and sometimes in fact embrace, launder, and then use.

But the effort in the AdvaMed frequently asked questions was one in which there was an effort to clarify the world of ASRs and was very unique in that AdvaMed actually reached out to the laboratory community and tried to get input from the laboratory community as well. So it's a very interesting starting point. They have put it officially on our docket, so I believe it's public. We do plan to steal the document probably to launder it and to try and use it as a basis for draft guidance to help clarify this colorful world.

It is a nuanced document that's missing some pieces. We might plug in those missing pieces, or try to at least. There continues to be a background of confusion and either inadvertent or deliberate misuse of ASR and home brew offering tests. Some of the home brew tests are actually going in ways I think even SACGT might not have predicted, some interesting ways.

So we are interested in continuing in a modest way to explore whether there are incremental changes in either the ASR exemption or the position itself. There is, as I suspect everyone in this room knows, a new face to the FDA administration. We have a new acting commissioner, we have a new head of general counsel, and we have a variety of new leaders in the deputy position in the Parklawn Central Commissions Office.

As far as I know, they haven't been asked the litmus request about abortion testing, and they also haven't been asked the litmus test about ASRs or home brew. So I have actually no way of predicting how any of this will come out.

Deborah Wolf was also sitting to the left of me. She's from the Office of Compliance, but we do operate as one operational unit in CDRH to take the lead in an ad hoc group that was a spinoff of this group to look at the colorful world of direct-to-consumer testing of genetic tests.

The notion was that FDA regulation of particularly the home brews, but even of the cleared and approved devices themselves is perhaps not the strongest regs that have ever been written in the history of U.S. regulatory authority. We were going to try to leverage off of FTC.

So we did put out a call for websites. We did get very interesting websites where there was direct-to-consumer testing, but we found this task to be much more challenging than we would have guessed. We were looking for two criteria. It had to be outrageous, but being outrageous wasn't enough. It had to be both outrageous and potentially harmful, because that's the way we interpret FTC's charge. Just being outrageous, fraudulent, or weird is not sufficient.

We actually had identified a couple of candidates, one in particular that we thought would be interesting to test the water. We had argued about how to craft the language so it would be friendly to a person who might not be a scientist. Actually, as only FDA can do, through several iterations, we were about to launch it to format when we noticed that either because of the business realities that were in the background, or maybe because FDA kept looking at the site, the site went out of business and put up a for sale sign.

(Laughter.)

DR. GUTMAN: Then at least one or two other sites that we were actively interested in started to change the tone of their advertisements in ways that made it seem to us that they were becoming more elusive.

So my request to you as a workgroup, not Emily's subgroup, but the workgroup, or frankly the audience as a whole, is if you have any favorite test you think is both outrageous but also dangerous that would be useful to us, this committee does exist. We are anxious to give Matt a little bit of extra work.

Mary Pastal on my staff and I both spent -- I was on an FDA-identifiable computer and she went on an anonymous computer, and we spent several hours one afternoon hunting, and maybe we didn't put in the right buzz words, maybe we're so stupid we don't know how to, you know, put DNA and test, or OTC and test, or DTC and test, or home use. We just couldn't find anything that piqued our interest. So I was surprised. Maybe we were just looking in the wrong places. This is an all points bulletin for help.

Two final notes. The diagnostic industry from my perspective has I think, probably a little bit rightfully, a sense of disenfranchisement, because pharma is bigger than they are, drugs makes a lot of money, and drugs are bigger than we are.

I had talked at an earlier meeting about our efforts to set up some kind of workgroup that might represent the old Pharmacogenomic Roundtable and be a little bit more distinctly IVD in orientation. I do think this committee -- and certainly I think we in drugs and diagnostics do appreciate a sort of shotgun or matchmaker role here in trying to bring culturally different companies together. Joe Hackett has set up a working group within our office, and is having active negotiations with Carolyn Jones and others in the industry. The notion is that we will, and I had hoped that we would have had this done by now, but there are a lot of competing demands on both industry's plate and our plate.

We do hope to at least explore whether there are opportunities for industry and FDA in a very diagnostic-specific way to describe the unique challenges that are on the table. And then it is worth noting, and I apologize I missed at least part of yesterday's activities, there really are fertile areas of development in ongoing work, that CDC has at least two initiatives. Muin's EGAPP and also Joe Boone's work in the area of trying to get material quality controls.

NIST has an activity where they are looking at now standards for proteomic testing, and AHRQ recently had a genomics workshop. They don't have a lot of money, but they have a lot of good ideas where there is interest in trying to step in and look at outrageous evidence-based medicine and outcomes.

Allen?