FDA's Current Approach to the Review, Labeling and Marketing of Genetic Tests
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So with that, let me introduce Dr. Steven Gutman, who is the head of our in vitro diagnostic office and who has responsibility for in vitro diagnostics throughout their whole life cycle.

DR. McCABE: Thank you. Again, we'll hold questions.

DR. GUTMAN: Good morning. As David has suggested, a fundamental tenet in our regulatory process is our regulation of labeling. So I'm going to surprise folks by sort of introducing labeling advertisement and future directions all in one fell swoop.

From our perspective, a label is a manufacturer's product monograph. It is what we refer to actually as a package insert, and it includes a wide range of both general and specific information about a device that allows the user to properly select and to properly use a device. The label is the basis for the approved promotion of the product by a manufacturer, and there is an important distinction here. Off-label promotion, off-label from the FDA-approved product, is not allowed, although off-label use is, of course, within the practice of medicine and at the behest of laboratorians or clinicians in fact is allowed.

FDA sets labeling requirements, monitors advertising and promotional labeling in the context of those labeling requirements, and watches to ensure that use is appropriate for its approvals. In vitro diagnostic devices are unique among medical devices in that we are so obsessed with labeling that we have our own regulation. We're the only product line with our own regulation. It appears in a glorious part of the regs called 809.10, which I suggest you all rush home and read.

(Laughter.)

DR. GUTMAN: It has 15 components, the most important of which is the intended use or the indication for use, since that particular component will determine the classification of the product and will determine where in Dr. Feigal's scheme a particular product will belong. The intended use may allow it to be Class I exempt, may require a Class II premarket notification or 510(k), or may be interesting and high risk and novel enough that it might require a Class III or PMA. So the intended use and the indications for use are really critical.

The IVD labeling regs are so brilliant that I intend to share them in their entirety with you this morning, albeit I will be mercifully brief and try to give you just a quick overview. They include the requirement for the proprietary name and establishment name for the product; the intended use or uses; a summary and explanation of the product and the principles involved in the device function; when appropriate, they require that there be information on reagents, information on instruments, or information on specimen collection, processing, storage, handling.

They include requirements for an outline of the procedure to be followed, an explanation for how results are calculated, and for us a very important feature, information on limitations of a device, either analytical or biological limitations. Then last but certainly not least, they include information on the expected values, on the heart and soul of the test itself, the performance

characteristics, and then as icing on the cake a bibliography, name and place of business, and a date of labeling so you know whether it's a contemporary label or not.

The FDA act itself does not define advertisement, but FDA interprets that term to include supplementary or explanatory information in relationship to the label, and products can be found misbranded if either the advertisement is false or misleading or the labeling is false or misleading.

The agency does watch to ensure that off-label use -- although perfectly appropriate by labs and physicians, we do watch to make sure off-label use is not promoted in device ads or labels. We have partners in crime, in particular in competitive areas, where in fact the manufacturers help us watch. We do not exert, as I think you already know, authority over laboratory ads or over laboratory reports, with the exception that in the ASR rule there is a requirement for a disclaimer clarifying who is taking responsibility for the performance of the in-house test made using the ASR, and there's also an opportunity for explanatory language explaining that you haven't grown a second head and you're taking advantage of a perfectly legitimate mechanism for generating a lab result.

The FDA, in fact, does not have direct authority over ads, does not have authority over marketing patterns, direct to consumers, and in fact the most interesting and strongest hook we have in this area is in the area of the ASR rule where we specifically note that an in-house test built with an ASR cannot be sold over the counter. The notion is that it's too complex a beast to be sold over the counter. As you'll probably hear more this afternoon, FTC has primary jurisdiction for over the counter devices, and it relates to an historic agreement, sort of like the Warsaw Pact but dating to 1954.

(Laughter.)

DR. GUTMAN: FDA does have guidelines for pharmaceuticals that are based on the requirement for truthful and balanced presentation of facts, and in fact if in that area there are violations identified, it could lead to misbranding charges. Those actually don't apply directly to diagnostic devices, but a lot of the principles are similar. So if one is looking for reasonable advice on honest labeling, that's probably as good a place to go as any.

There are two general important themes at FDA. They're not new but they're certainly prominent in the life of our center and the life of our agency. The first is an increased flexibility in regulatory approaches and an increased menu of regulatory tools, and I won't dwell on them because they're somewhat an arcane and parochial taste, but in fact there are alternatives now to the 510(k) process that provide opportunities for more streamlined submissions, there are alternatives to the PMA process that allow for administratively more controlled patterns of interaction with the agency, there are new mechanisms for making classifications simpler so that we can classify important novel devices with more facility than in the past, and there is, of course, as a result of the modernization act, a commitment on the part of the agency, and certainly on the part of the center, to be least burdensome and to make sure that our premarket review process is focused on relevant endpoints and doesn't wander into interesting academic escapades.

The second equally important theme and a slightly newer theme is derived from senior management in the Center for Devices, and that is the strategic plan which emphasizes the notion that we as regulators should take a very broad view of regulation and we should, in fact, approach regulation from a pan-regulatory standpoint rather than some kind of segmented, separated, pre- and post- and safety patient piece, that we should really bundle that together into what we call the total product life cycle, an entity which charts products -- and Dr. Feigal showed you in glorious

graphical form -- charts them from birth to obsolescence and watches as you build on existing knowledge, so better knowledge management.

What has happened that is certainly unique in IVDs -- I would contend lots of things are rather unique about IVDs, but certainly what's happened that's unique in IVDs is that we have in the center under Dr. Feigal's charge crafted a single office in which all regulatory functions are now subsumed. So the Office of In Vitro Diagnostics is responsible for premarket review, it's responsible for compliance activities, it's responsible for postmarket surveillance, and you have truly for internal and external stakeholders an organization which is in the pursuit of providing one-stop shopping.

As you are all aware from the last meeting, or maybe from previous meetings, the Secretary's Advisory Committee on Genetic Tests, your predecessor committee, put forth a challenging menu of ideas for HHS to consider for enhancements and oversight by, frankly, all of the involved regulatory parties -- CMS, FDA, and even CDC, which isn't exactly a regulatory party.

FDA in this scheme was charged with considering increased oversight of new genetics tests, and although SACGT was bold, they weren't completely crazy, so they in fact suggested that this ought to be risk based, that this ought to be posited in a way that would be non-chilling to technology, and that this be informed by professional societies. Whatever else, I do know it's certainly the intention of the agency as it explores this area to follow those central tenets.

Probably one of the most interesting work products of the Secretary's Advisory Committee was a data template generated by the data collection subgroup that was chaired by Wylie Burke. I think it is well known, but if it's not then I will make it well known that that template was explored in the context of a professional roundtable and that the Association of Molecular Pathologists were in fact the sponsors of that roundtable, and Dr. Leonard in fact was the chair of what turned out to be two merged committees that created a data collection template that was designed to try to tame this data set.

What the agency has done is it has simplified and modified that template and in fact is now using an FDA model for that template in the course of its routine reviews. So perhaps one size does or perhaps it doesn't quite fit all. So I'm not sure what we gave to SACGT, but I am quite certain of what we took away from SACGT, and what we took away from SACGT was the notion that there ought to be some kind of streamlined and standardized way of presenting data about laboratory tests.

We in fact adopted a review template. It has essentially the heart and soul of the FDA review process subsumed in that template, and it has replaced our final review memos, and most recently it is now being made public. So if you bother to go on the OIVD webpage and look at products that have been cleared, you'll see some have the decision template and some don't, but hopefully in a month or two they will all have that decision template.

What we settled on was a template which included key administrative information, like the 510(k) number, the analyte, the type of test, who was submitting the test and what its names were; the key regulatory information, which includes intended use; device description; the charting of the critical element, which is substantial equivalence, which Dr. Feigal mentioned; any standards or guidances referenced to help make that decision; the heart and soul of the review processes, which is looking at the scientific information to see if it does what it says it does, so looking at test principles and performance characteristics. Performance characteristics is the single longest part of any subcomponent of this template, as you might gather, since it attempts to encompass all

the features of performance. A conclusion, and I guess not entirely scientific but supporting information and contact information.

The future is now. So although it's a tool that we'd like to explore in the future, we are now using it to try and tame our process, to try and standardize our process, to try and streamline our process, and certainly to make our process of premarket review transparent.

We view this review template as an IRS 1040, as the final report, and it is our intent at some point to steal from TurboTax or TaxCut the idea that they are probably making lots of money off of -- I hope so, since it was a great idea -- the idea of an electronic format that would streamline input from manufacturers and streamline the review process for FDA. So we have a -- I wouldn't call it long term, but certainly I also would not call it a short-term project to try and craft an electronic format that would allow this data template to be based on Schedule A and Schedule B and Schedule C and all kinds of special forms, when appropriate.

In the interim, we actually have as a short-term project -- that's three months, but of course in the FDA that really means six or seven months -- the intention of producing a paper-based version. So we're going to create our 1040 the old-fashioned way, using paper, and we'll fool around with that before we actually generate electronic signals. I spend a lot of time in this review because I love this template. It is a gift that SACGT gave to the agency, and it may or may not be useful for future genetic regulation.

The most interesting development on the sidelines, as I suspect many of you know, has been in recent months commercialization of microarrays and other technologies which may challenge the definition of the ASR, and certainly challenge the definition of Class I ASRs. In the light of those technologies, and in the light of revisiting the ASR rule as a fundamental tenet, we in fact are doing a great deal of policy and legal analysis to try and figure out how all this sorts out. Under the statute, all new devices actually come to life as Class III products. That's the natural default. The ASR is one type of new device, and if a product in fact fits into that category, the ASR has historically, with a few exceptions as David pointed out, been viewed as a Class I exempt device.

Some of the new technology, some of the microarray technologies, whether ASRs or not, may not be Class I exempt, particularly if they fall outside of the description of what we would consider a Class I product, and in fact what I may not have shared with this group before because it's actually a relatively new discovery on my part -- you see, all devices have limitations. Those limitations are in fact visited in the law, and if you're really perverse you can actually look it up. It's 510(l) of the law. They are present in the regulations, and if you really have a pension for joy, it's in 864.9 of the regulations.

What they suggest is that some new technologies may not fit the description of ASR classifications or of Class I exempt classifications and may trip the limitations, and I'll give you two examples that might trip the limitations. The limitations of an exempt product might be tripped if you had a startling new technology, or it might be tripped if you had interesting new intended uses.

So we are exploring that, and it's certainly our intention, once we have more clarity on exactly what those words mean, to try and communicate that to both the laboratory and the manufacturing communities.

We are revisiting the ASRs, and it's been tougher than I would have hoped, certainly tougher than I would have guessed, but that revisit follows some of the tenets that we've always expressed,

which is that we want this to be collaborative with other parts of HHS. I don't remember if I've expressed it or not, but in fact the revisit of ASRs is not focused on genetic testing alone. That is, we went back and looked at the issue critically. We in fact concluded that there actually was a good argument to make for not treating tests that were genetic-based in some exceptional way, that all tests ought to be created and treated equally, and they ought to be treated in the context of the risk they pose.

So the one really big change as we revisit the ASRs is not focused only on genetics tests but on any test, frankly. And it's likely as we struggle forward with this that we will be emphasizing the Commissioner's goal of risk-based and cost-effective regulation that will likely emphasize the Commissioner's goal of informed consumers. That certainly is at the heart of the data template we're now posting, and it is, for better or worse, likely to take time. It's likely to take time because if there's anything that we have learned, it's that these issues are challenging.

The central issue is trying to develop a risk-based approach towards the ASRs. That was a challenging issue for SACGT. SACGT, in fact, drew back after a number of efforts to try and craft a variety of very rich and nuanced risk schemes. That turns out to be a challenging issue for FDA in spite of our experience, and we have lots of experience classifying products and lots of experience with risk management. It is harder than I would have guessed to sort through and craft a non-chilling, a risk-based, and a user-friendly mechanism for dealing with this challenging problem.

We are expecting input from professional groups. I'm personally going to nag some of those professional groups at the break today. Input is still welcome, and any help in trying to move forward with an intelligent, well-crafted regulatory scheme that informs public health would be welcome.

Thank you.