FDA-approved IHC tests.[3] Also, if an FDA IHC kit is modified from the specified protocol, including a customized interpretation that subtracts normal tissue staining in the evaluation of the slide, the test becomes an in-house validated assay since it is not used as approved by the FDA.

The economic conclusions represented by the authors are also of concern. They were based on reagents that are much less expensive than HercepTest. Furthermore, the direct costs of any *HER-2* laboratory test become almost trivial when weighed against the enormous total costs incurred in managing a patient treated with trastuzumab.

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In Reply: Drs Tubbs and Hicks argue that because of our deviation from the FDA-approved guidelines our test "becomes an in-house validated assay." We would first point out that the guidelines themselves have limitations, of which the FDA itself appears aware. In a recent briefing document, the FDA submitted that "the clinical benefit of trastuzumab was primarily seen in patients whose tumors were scored as IHC 3+."[1] But the FDA included the 2+ subgroup with the 3+ group for consideration for trastuzumab therapy. Subsequently, pivotal studies like that of Tubbs et al[2] showed that most of the 2+ scores by IHC are essentially false-positive. This supports the FDA Drug Advisory Committee's initial predictions that the 2+ score may not be associated with the desired response to trastuzumab. Nonetheless, the FDA has not eliminated the 2+ score result as a requirement for eligibility to trastuzumab treatment despite evidence to the contrary.

Regarding our methods, the A0485 monoclonal antibody we used is the exact antibody in the FDA-approved HercepTest kit, and we also used the same polymer detection system included in the kit. The only notable deviation from the HercepTest is the subtraction scoring, which we previously documented significantly improves the specificity of HercepTest.[3] With respect to modification of the FDA guideline for test method, the boiling water temperature in a laboratory in Denver where the altitude is around 5000 feet is significantly different from a laboratory in Miami. This would force the Denver laboratory to modify the boiling temperature setting described in the FDA guidelines.[4] Thus, deviation from the FDA-approved guidelines is not only acceptable but may be necessary at times to maintain high levels of accuracy and precision, provided it is justified on a large-scale quality control program.

Economically, the IHC direct cost to our laboratory would be comparable with that of HercepTest, especially since our estimated FISH cost that we published in the study was conservative, excluding control testing and repeated tests due to failure. Drs Tubbs and Hicks' statement about the cost of trastuzumab treatment is well taken. It is worth remembering, however, that our cost analysis was based on the use of FISH as a *screening* test. Because of the 20% to 25% overexpression rate for *HER-2* in invasive breast cancer, there would be 4 to 5 times as many patients tested by FISH than would be FISH-positive (trastuzumab-eligible) in this scenario. The point we tried to highlight in our study is that an optimized quality assurance and quality control program would nullify the need for the expensive FISH test for screening, regardless of the treatment costs.

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RESEARCH LETTER

Tramadol Abuse and Dependence Among Physicians

To the Editor: Historically, new opioid pain medications have been introduced as having low abuse liability and then later found to have significant risk. Tramadol achieves its analgesic activity from an M1 metabolite with potent opioid properties and through inhibition of reuptake of monoamines.[1] Following release of this product, reports of tramadol abuse began to occur and package insert warnings regarding abuse have been heightened 3 times. The US Food and Drug Administration's (FDA's) MEDWATCH system has received hundreds of spontaneous reports of tramadol-associated abuse, dependence, and withdrawal.[2] Among individual opioids listed

in the 2001 and 2002 annual reports of the American Association of Poison Control Centers Toxic Exposure Surveillance System, tramadol ranked second to oxycodone in number of exposure cases.[3] Other reports, sponsored by the manufacturer, have suggested low abuse liability; however, their conclusions are problematic due to methodologic issues. For example, in 1 report[4] the total number of physicians admitting abuse of tramadol was divided by the total number of physicians being monitored, without measuring the percent of these physicians actually taking the drug. In April 1998 the FDA cited the lack of comparative data as a major reason for the committee's decision to not recommend scheduling tramadol.[5] The present study reports relative frequency of tramadol abuse compared with other drugs.

Methods. Records of all physicians monitored in the Alabama Physician Health Program and the Michigan Health Professionals Recovery Program 1994-2002 were analyzed for all drugs mentioned. Physicians were referred to these programs because of concerns regarding substance abuse and all underwent evaluation and treatment and participated in monitoring. In reviewing their records, 3 distinct categories of tramadol abuse were noted: (1) primary tramadol dependence included cases in which tramadol was the sole drug or the initial drug of choice; (2) tramadol relapse included cases in which an individual was in remission from previous addiction but relapsed to addictive drug use involving tramadol; and (3) tramadol substitution categorized individuals who used tramadol when their primary drug of abuse was not available or as an attempted self-detoxification. The study received a waiver from the ethics committee of the Medical Association of the State of Alabama.

Results. Five hundred ninety-five records were reviewed and 872 drug mentions were found. Opioids were mentioned second only to alcohol (TABLE). Among opioids tramadol was the third most frequently mentioned. Tramadol accounted for 10% of all opioid mentions, exceeding those of fentanyl, codeine, propoxyphene, oxycodone, morphine, and butorphanol.

Of the 33 physicians who mentioned tramadol, 32 had a diagnosis of substance dependence, and 1 had a diagnosis of substance abuse. The frequency of the 3 patterns of tramadol abuse were: primary tramadol abuse (24%), relapse associated with tramadol use (42%), substitution of tramadol for the drug of choice (30%), and unknown (3%).

Comment. Tramadol was mentioned relatively frequently as a drug abused by physicians, although it was rarely the primary drug of choice. The finding that tramadol was mentioned more frequently than fentanyl, oxycodone, dilaudid, and other known highly addictive opioids could be explained by an intrinsic abuse liability that was higher than previously thought. Alternatively, its availability and lack of being scheduled under the Controlled Substances Act could make it more attractive as a drug of abuse. Concerns regarding toxicity relate not only to abuse potential but also to seizures related to excessive dosage and to respiratory depression and risk of fatal overdose, a risk common to other opiates. More recently tramadol has been released in combination with acetaminophen, raising concern about liver toxicity with overdose. An important limitation of this study is that it did not attempt to examine the proportion of physicians actually exposed to each opioid who develop abuse or dependence. However, given the frequency of its mentioned abuse, physicians should be aware of this risk.

Table. Drugs Abused by Physicians in Alabama and Michigan, by Category

Substance	No. of Mentions		
	Alabama	Michigan	Total
Alcohol	191	198	**389**
Opioids	190	146	**336**
Hydrocodone	86	53	**139**
Meperidine	25	10	**35**
Tramadol	23	10	**33**
Fentanyl	11	16	**27**
Codeine	11	13	**24**
Propoxyphene	10	6	**16**
Oxycodone	10	5	**15**
Morphine	8	4	**12**
Butorphanol	5	7	**12**
Pentazocine	0	9	**9**
Other	0	14	**14**
Sedatives	59	10	**69**
Stimulants	34	21	**55**
Marijuana	12	11	**23**

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Access to Data: Dr Skipper had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analyses.

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