United States Court of Appeals
For the First Circuit

No. 00-1158

UNITED STATES,

Appellee,

v.

DAVID W. PRIGMORE,

Defendant, Appellant,

No. 00-1229

UNITED STATES,

Appellee,

v.

LEE H. LEICHTER

Defendant, Appellant,

No. 00-1230

UNITED STATES,

Appellee,

v.

JOHN F. CVINAR,

Defendant, Appellant.

APPEALS FROM THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF MASSACHUSETTS

[Hon. Joseph L. Tauro, U.S. District Judge]

Before

Selya, Circuit Judge,
Coffin, Senior Circuit Judge,
and Stahl, Circuit Judge.

Richard G. Taranto, with whom Farr & Taranto, Andrew Good, Harvey A. Silverglate, Silverglate & Good, William H. Kettlewell, Michael B. Galvin, Dwyer & Collora, LLP, Robert D. Keefe, Daniel W. Halston, Jason T. Sherwood, and Hale and Dorr LLP, were on brief, for appellants.

David S. Kris, Attorney, Department of Justice, with whom David S. Mackey, Acting United States Attorney, Stephen A. Higginson, Special Assistant United States Attorney, and Michael K. Loucks, Assistant United States Attorney, were on brief, for appellee.

March 16, 2001

STAHL, Circuit Judge. On August 24, 1995, after a twenty-seven day trial, a jury convicted defendants-appellants Lee H. Leichter, John F. Cvinar, and David W. Prigmore of conspiring to defraud and impair the functioning of the United States Food and Drug Administration (FDA) in connection with its oversight and regulation of medical devices. See 18 U.S.C. § 371. The jury simultaneously acquitted George Maloney and Kenneth Thurston of the same charge. The district court thereafter sentenced each convicted defendant to 18 months' imprisonment and two years of supervised release, but stayed execution of the sentences pending appeals. In these appeals, Leichter, Cvinar, and Prigmore ("defendants") raise a host of arguments challenging the legality of their convictions. In addition, Prigmore claims that insufficient evidence supports his conviction and that his sentence is unlawful. We vacate the convictions and remand for further proceedings.

I.

Because we review the trial record primarily to ascertain whether an error in the district court's jury instructions was harmless, see infra Section II, we look at the evidence as a whole and not in the light most favorable to the government, see Arrieta-Agressot v. United States, 3 F.3d 525, 528 (1st Cir. 1993). Thus, although we give a detailed account

of the evidence the government relies on to support its case theory and harmless-error argument, we also provide an overview of relevant responsive evidence and arguments. See id. at 528-29. We note too that this case has a complicated procedural history which we describe only insofar as is relevant to these appeals. Readers interested in additional procedural background should consult our previous opinion in this matter. See United States v. Leichter, 160 F.3d 33, 34 (1st Cir. 1998).

A. Statutory and Regulatory Background

In 1976, Congress amended the Food, Drug, and Cosmetics Act (FDCA), 21 U.S.C. § 360 et seq., by passing what it denominated the Medical Device Amendments (MDA), 21 U.S.C. § 360c et seq. The amendments made the FDA responsible for ensuring the safety and effectiveness of medical devices distributed to the American public. This prosecution proceeded on the theory that, in testing and marketing medical devices known as "heart catheters," the defendants conspired to violate provisions of these statutes and regulations promulgated thereunder.

A heart catheter is a tiny instrument consisting primarily of a thin metal wire with a small inflatable balloon at or near one end. The device is used in a surgical procedure called angioplasty, which seeks to treat heart disease by

opening clogged coronary arteries. During angioplasty, a physician inserts a heart catheter into a patient's body, typically through an artery in the leg or groin area. The physician then steers the device through the patient's circulatory system to the site of the blockage and inflates the balloon with fluid. As it is inflated, the balloon breaks the "plaque" that is clogging the artery and pushes it against the artery wall. The physician subsequently withdraws the liquid, deflates the balloon, and removes it and the catheter, thereby allowing blood to flow freely through the artery.

Regulations promulgated pursuant to the FDCA and MDA designate heart catheters as Class III medical devices. See generally 21 C.F.R. Part 870. Class III medical devices are the most heavily regulated medical devices in the country. See 21 U.S.C. § 360c(a). Before a manufacturer may market a new Class III medical device, the manufacturer must apply for and receive "premarket approval" (PMA) from the FDA. 21 U.S.C. § 360c(a)(C). In connection with its PMA application, the manufacturer must submit information sufficient to provide the FDA with "reasonable assurance" that, inter alia, the device is both "safe" and "effective." 21 U.S.C. § 360e(d)(2).

Under the MDA,

> [T]he safety and effectiveness of a [Class III] device are to be determined –

> (A) with respect to the persons for whose use the device is represented or intended,
>
> (B) with respect to the conditions of use prescribed, recommended, or suggested in the labeling of the device, and
>
> (C) weighing any probable benefit to health from use of the device against any probable risk of injury or illness from such use.

21 U.S.C. § 360c(a)(2). Regulations promulgated pursuant to this statute (and others) elaborate:

> In determining the safety and effectiveness of a device for purposes of [deciding whether to grant] . . . premarket approval of class III devices, the Commissioner . . . will consider the following, among other relevant factors: (1) The persons for whose use the device is represented or intended; (2) The conditions of use for the device, including conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use; (3) The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and (4) The reliability of the device.

21 C.F.R. § 860.7(b).

> There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by

> adequate directions and warnings against unsafe use, outweigh any probable risks.

Id. § 860.7(d)(1).

> There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the targeted population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Id. § 860.7(e)(1).

Two additional sets of regulations governing Class III surgical devices are of particular importance to this case, so we describe them in some detail. The first requires, insofar as is relevant, that a manufacturer of a previously approved Class III surgical device "submit a PMA supplement for review and approval by FDA before making a change affecting the safety or effectiveness of the device . . . ." 21 C.F.R. § 814.39(a). As with an application for initial PMA, the so-called "PMA supplement" must contain scientific information that provides a basis for approval of the modified device. See id. § 814.39(c). The regulation lists eight "types of changes" for which a PMA supplement must be filed "if [the changes] affect the safety or effectiveness of the device," id. § 814.39(a), including the following: "[n]ew indications for use of the device," id.

§ 814.39(a)(1); "[t]he use of a different facility or establishment to manufacture, process, or package the device," id. § 814.39(a)(3); and "[c]hanges in the performance or design specifications, circuits, components, ingredients, principle of operation, or physical layout of the device," id. § 814.39(a)(7). By operation of § 814.39(c) ("All procedures and actions that apply to [a PMA] application under § 814.20 also apply to PMA supplements . . ."), the manufacturer also must "periodically update [a] pending [PMA] application with new safety and effectiveness information learned about the device from on-going or completed studies that may reasonably affect an evaluation of the safety or effectiveness of the device . . . ." Id. § 814.20(e).

As implied by the regulations just quoted, a manufacturer need not submit a PMA supplement "if the change does not affect the device's safety and effectiveness . . ., e.g., an editorial change in labeling which does not affect the safety or effectiveness of the device." Id. § 814.39(b). But where the FDA has required periodic reports as a condition of approval of the device, the manufacturer must report any changes to the FDA "in [its] postapproval periodic reports . . . ." Id. The PMAs of the heart catheters at issue in this case explicitly

required postapproval reports documenting any and all changes to the catheters.

The second set of regulations underlying this prosecution arise from the background fact that, prior to submitting a PMA application or PMA supplement, the manufacturer of a new or modified Class III medical device may desire to test the device in humans. To do so lawfully, the manufacturer must apply to the FDA for an "investigational device exemption" (IDE). An IDE "permits a device that otherwise would be required . . . to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device." 21 C.F.R. § 812.1(a). An IDE thus permits limited use of an unapproved device for the purpose of collecting human test data. See id. But the testing regulations themselves specify a number of situations in which an IDE is not a prerequisite to the investigational use of unapproved Class III medical devices in humans. See id. § 812.2(a), (c). Such "exempted investigations" include "consumer preference testing" and the "testing of a modification" to an approved Class III medical device, so long as "the testing is not for the purpose of determining [the unapproved device's] safety or effectiveness and does not put subjects at risk." Id. § 812.2(c)(4).

B. Relevant Factual Background

Defendants had leadership positions at United States Catheter and Instrument, Inc. (USCI), a division of C.R. Bard, Inc. (Bard), for most or all of the alleged conspiracy period, which ran from 1987 to 1990. Defendant Leichter was USCI's head of regulatory affairs and quality assurance; defendant Cvinar was USCI's president; and defendant Prigmore, who previously had been president of USCI, was until September 1989 a vice president at Bard with authority over USCI's operations. All three defendants had offices in Billerica, Massachusetts, where USCI operated a manufacturing plant and maintained its corporate headquarters.

USCI's chief decision-making body was its Management Board. Cvinar presided over the Board and Leichter was a member. Cvinar reported to Prigmore. Representatives from middle management at USCI made up an organization known as the "Breakfast Club." The Breakfast Club reported regularly to the Board and provided the Board with the minutes of its meetings. The Breakfast Club had no authority to make decisions without the Board's approval. Leichter was not a member of the Breakfast Club, but he sometimes attended its meetings.

The conspiracy alleged in this case involved two lines of heart catheters manufactured by USCI. In 1987, USCI

introduced the first line, which we shall call the "Probe Line," with a catheter known as "Probe A." In 1988, USCI modified Probe A and renamed it "Probe B." In early 1989, USCI began distributing Probe B commercially. Later in 1989, USCI modified Probe B and renamed it "Probe C." At trial, the government's conspiracy theory with respect to the Probe Line was that, under defendants' leadership and with defendants' knowledge and approval, USCI tested Probe B and Probe C in humans in violation of the Class III medical device testing regulations; marketed Probe B and Probe C in violation of the Class III medical device marketing regulations; and otherwise deceived the FDA in order to avoid the agency's oversight.

In 1987, the second line of heart catheters, which we shall call the "Miniprofile Line," featured a catheter called the "Simplus." In 1988, the Simplus evolved into a catheter called the "Miniprofile," which, in 1989, evolved into a catheter called the "Solo." In 1989, USCI also filed a PMA supplement for a catheter called the "Solo Sr.," but the company never manufactured the Solo Sr. and ultimately withdrew the filing. With respect to the Miniprofile Line, the government's conspiracy theory once again was that, under defendants' leadership and with defendants' knowledge and approval, USCI committed a number of violations of the Class III medical device

testing and marketing regulations and otherwise lied to the FDA to avoid the agency's oversight. The following is a summary of the evidence supporting the government's conspiracy theories.

1. The Probe Line

In the early 1980s, when angioplasty first became available in this country, USCI controlled 100% of the market for heart catheters. By the late 1980s, however, USCI's market share had declined by about half and the market had become very competitive. When USCI introduced the FDA-approved Probe A in 1987, the device initially sold very well. But the device had a significant limitation. Although USCI marketed Probe A with a label warning that it should not be rotated more than one full turn (360 degrees) in the same direction, physicians performing angioplasties sometimes saw it as necessary to rotate the device beyond its warned-against limitation. When this occurred, the device's balloon had a tendency to wrap itself around the wire, which prevented deflation. This, in turn, blocked blood flow through the artery and complicated efforts to remove the device from the body.

USCI's solution to Probe A's wrapping problem was Probe B, a redesigned version of the same catheter. In Probe A, the balloon attached at the end of the wire, but in Probe B, the balloon attached to a polymer tube threaded over the wire. The

result was that Probe B could be rotated more than once in the same direction without the balloon becoming entangled. Unfortunately, however, the new design created different problems.

There was evidence that, in actual use in humans, Probe B's wire broke 25 times more frequently than Probe A's wire. There also was evidence that, when compared to Probe A, these breaks were far more likely to occur when the device was rotated more than once in the same direction. Moreover, the consequences of a Probe B wire break tended to be more serious. In the relatively unlikely event of a Probe A wire break, the catheter's metal tip typically would not detach and could be removed with the wire and balloon. By contrast, when Probe B broke, the broken tip frequently could not be removed with the rest of the catheter. In such a situation, the physician either had to leave the tip in the patient or remove it by invasive surgery. Evidence of these problems poured into USCI in early 1989, but, contrary to the urgings of certain USCI "Crisis Team" members appointed by Cvinar to handle the situation, USCI, and then Bard, declined to order a voluntary recall of Probe B.

The government contends that this disastrous state of affairs was a direct result of USCI violating the regulations governing the testing and marketing of Class III medical devices

in connection with bringing Probe B to market. We start with a synopsis of the evidence of unlawful testing in connection with Probe B.

a. Misconduct Involving the Probe B

On November 11, 1988, one of Leichter's subordinates filed a PMA supplement for Probe B asserting that it should be approved without being tested in humans. Upon receipt of the supplement, the FDA questioned USCI's assertion and asked for proof that clinical testing was unnecessary. In a December 13, 1988 letter and in a December 15, 1988 meeting, certain of Leichter's subordinates explained to FDA representatives that Probe B's safety and effectiveness had been established by laboratory "bench" testing and that the FDA could rely on data submitted in connection with Probe A's PMA application because the two devices were similar. The December 13 letter also explained that clinical testing was not necessary because bench testing had showed that Probe B "allows for more independent rotation of the core wire and balloon" than Probe A. Leichter sent the Management Board a copy of the December 13 letter and a memorandum summarizing the December 15 meeting. On these documents he handwrote "Excellent work." On January 19, 1989, the FDA approved Probe B for commercial distribution without requiring testing in humans.

In fact, however, notwithstanding its representations to the FDA and without having applied for an IDE, in late October 1988, USCI began shipping Probe B catheters for purposes of gathering feedback as to how they performed in humans. Documentary evidence suggests that this feedback gathering, which USCI called "disaster checking," was for purposes of ascertaining Probe B's rotational capabilities, steerability, and "performance characteristics . . . as compared to the [Probe A]." The government contends that testing for such purposes was safety or effectiveness testing, and thus violated a negative implication to be found in the Class III medical device testing regulations: that an unapproved Class III medical device may not be tested in humans for safety or effectiveness without an IDE. See generally 21 C.F.R. Part 812. With the exception of Prigmore, who explicitly challenges the sufficiency of the government's proof linking him with this evidence, defendants do not dispute that they were aware of and approved of this course of conduct. Rather, pointing to testimonial evidence supporting their case theory, they (joined by Prigmore arguing in the alternative) take the position that this "testing" was solely for purposes of establishing consumer preferences; was not for purposes of determining safety or effectiveness as defendants reasonably understood the regulations to define those terms; and

did not pose risks to humans beyond those associated with Probe A. Defendants thus understood the testing to be exempted from Part 812's IDE requirements by § 812.2(c)(4). We shall have considerably more to say on the defendants' understanding of Part 812 and the terms "safety" and "effectiveness" later in this opinion.

The government also argues that, in bringing Probe B to market, USCI violated the Class III medical device marketing violations in two ways. First, USCI failed to report to the FDA that it was conducting clinical tests in humans in several documents: the Probe B PMA supplement (which was filed after clinical tests in humans began in October 1988); the December 13, 1988 letter to the FDA; the December 15, 1988 meeting with FDA representatives; and the subsequent updates required by the FDA when it approved Probe A. See 21 C.F.R. §§ 814.39(c), 814.20(e). Moreover, USCI failed to report that, in Probe B's clinical tests, the device experienced breakage rates far beyond those reported with respect to Probe A as marketed. See id. Here too, only Prigmore disputes the sufficiency of the evidence that he was aware of Probe B's test results and the subsequent failure to share those results with the FDA; the other defendants take the position that, under their understanding of

the regulatory mandates and the typical circumstances of a Probe B tip break, no reporting was required.

Second, USCI representatives were marketing Probe B with the claim that it could be rotated more than once in the same direction even though Probe B's PMA supplement represented that the device would retain Probe A's label warning against more than a single revolution. There was evidence that, despite the label warning, the device was presented to USCI sales staff as the solution to Probe A's rotational limitations. Presentations to sales staff at the company's annual national meeting held at Lake Tahoe, California, from January 15-17, 1989, left at least one salesman with the impression that "Probe B could be torqued more than once, and that was the whole idea of freeing the wire [from the balloon]." Also, written promotional materials for Probe B explained that "[t]his new device allows increased torque delivery because of the new design" and that "with every rotation, it's the wire you're steering and not the balloon." In addition, a USCI videotape designed to instruct doctors on use of Probe B contained remarks from a doctor suggesting that the device could be rotated two or three times.

USCI's sales force, which had been instructed to warn physicians against overrotation of Probe A, were not so

instructed with respect to Probe B. Indeed, USCI sales staff informed physicians that, although there would be no labeling change, Probe B contained improvements "that should prevent the twisting problem" that occurred with overrotation of Probe A. One USCI representative told a doctor that he could rotate Probe B as many as 10 times, and another told several doctors at a physicians' conference that they could rotate the device up to 15 times (although the second representative subsequently was admonished not to advocate such extreme use).

Defendants do not contest that USCI representatives in fact told physicians that they could rotate Probe B more than once, and that USCI promotional materials might have given the same impression. Defendants vigorously contest, however, that they themselves knew of and condoned promotion of Probe B contrary to its label warning. The evidence as to defendants' knowledge and condonation was thin; Cvinar and Prigmore attended the January 1989 Lake Tahoe conference, but no witness placed them at the presentation in question. All promotional materials relating to use of a Class III device were approved by the regulatory affairs department (which Leichter headed), but there was evidence that the doctor's remarks on the videotape were added after regulatory affairs had approved it. In any event, no witness or document ever directly tied defendants to the

promotional materials in question. Finally, there was evidence that Leichter insisted that label warnings be followed when he learned that some USCI salespeople had been promoting Probe B contrary to its label warnings.

b. Misconduct Involving the Probe C

The government asserts that USCI committed similar regulatory infractions with respect to the testing and marketing of Probe C. In early 1989, at the same time the Crisis Team was reacting to the problems with Probe B, USCI was working urgently on modifications designed to rectify those problems. The result was Probe C. USCI bench tested eight Probe C prototypes and, without having secured an IDE from the FDA, shipped two or three of the prototypes for use in humans to see whether the changes improved the strength of the catheter's tip and thus reduced the chance of breakage. Some of the prototypes used in humans did not perform as well as Probe B, but, by March 1989, USCI had settled on a final version. In this version, USCI increased the diameter of the device's core wire by 30% and eliminated a solder joint used to attach the wire to a spring. USCI also modified the device's assembly process.

USCI then marketed Probe C without filing a PMA supplement. In fact, the company took steps that can be taken to evince an intent to conceal Probe C’s changes and thus to

blur the differences between Probe C and its predecessor. For example, USCI basically retained the Probe B label for the new device but placed on the label an inconspicuous dot or small letter "C" so that USCI, and USCI alone, would know the model's identity. In the government's view, the unapproved testing and marketing of Probe C was unlawful because the testing was for purposes of establishing the device's safety or effectiveness, see 21 C.F.R. Part 812, and because the new product contained design changes affecting its safety or effectiveness, see id. § 814.39(a), (b). Once more, Prigmore contests the sufficiency of the evidence establishing his knowledge and approval of USCI's conduct with respect to Probe C, and the other defendants assert that their conduct was perfectly lawful under their understanding of the applicable regulations.

c. Additional Deceptions

In the spring of 1989, the FDA learned that USCI had modified Probe B so as to create Probe C without filing a PMA supplement. At the same time, the FDA came into possession of information that caused it to become concerned about Probe B tip breaks. On April 25, 1989, an FDA reviewer met with Leichter and informed him that she was concerned whether Probe B was sufficiently safe. Leichter denied that there were safety concerns and failed to reveal the tip breaks that had occurred

during the investigational use of Probe B in humans. The next day, Prigmore sent Leichter a memo conveying a "personal 'job well done' with regard to your recent dealings on the Probe, and particularly your meeting with the FDA."

The FDA later requested explanations for both Probe B's failure rates and USCI's failure to file a PMA supplement with respect to Probe C. On May 15, 1989, USCI responded to the FDA's concerns by letter. All three defendants spent several hours reviewing the contents of the letter. The letter explained that, following field observation and analysis of broken catheters, it had become clear to USCI that Probe B's breakage problems were attributable to "overtorque[ing] during clinical use while the tip was restricted." In other words, the device was only breaking when it was being used contrary to its label warning against more than a single revolution in either direction. The letter also took the position that Probe B was sufficiently safe because the device's actual breakage rate was statistically identical to the breakage rate of Probe A observed in clinical testing and reported to the FDA before the agency acted favorably on the Probe A PMA application. But the letter did not reveal that the tip of Probe B had a tendency to remain in the patient following a break. Nor did it acknowledge that, in actual use, Probe B in fact broke 25 times more frequently

than did Probe A, and that, during what defendants call the "consumer preference testing" of Probe B, the device broke many times more frequently than did Probe A in actual use. Defendants contend that, under their understanding of the regulations and the circumstances of Probe B tip breaks, none of the foregoing representations or omissions was fraudulent.

The letter also explained that, although the design modifications in Probe C "substantially reduced the risk of critical tip failure," these modifications did not affect the device's safety or effectiveness. The asserted basis for these seemingly contradictory assertions was a tripartite argument: (1) the regulations only require the filing of a PMA supplement when a design modification affects the safety or effectiveness of the device when it is used in accordance with its labeling; (2) the modifications to Probe B inhering in Probe C only affected (by improving) the safety and effectiveness of the device when it was used in a manner contrary to its labeling (i.e., when, contrary to its label warning, the device was rotated more than a single revolution in the same direction); and (3) the modified catheter that became Probe C thus could be marketed without a PMA supplement. This argument presaged defendants' trial position in the dispute about the meaning of the regulations at the core of this case.

On June 9, 1989, the FDA ordered a recall of Probes B and C and directed USCI to file a PMA supplement before marketing Probe C in the future. In August 1989, USCI submitted such a supplement. In the supplement, USCI asserted that the Probe C was in fact safe and effective and cited in support of this claim the data gathered during its earlier investigational use of the device in humans, along with additional follow-up data collected at the direction of the FDA. The PMA supplement stated without limitation that Probe C had been "distributed from March 1989 until August 1989" in order "to determine the safety and efficacy of the device."

2. The Miniprofile Line

During the conspiracy period, the Miniprofile line was USCI's second most profitable line of catheters, ranking just behind the Probe line in sales. At trial, the government introduced evidence tending to show that, with defendants' knowledge and approval, USCI engaged in four courses of conduct with respect to the Miniprofile line that the government sees as fraudulent: (1) in late 1987, USCI changed the manufacturing location for the Miniprofile line and then marketed catheters manufactured at the new location without obtaining the FDA's prior approval; (2) in 1988, USCI modified the design of the Miniprofile, tested the modified catheter in humans without

having secured an IDE, marketed the modified version without having filed a PMA supplement, and adopted complex inventory sorting and labeling methods designed to conceal the change; (3) in 1989, in PMA supplements filed in connection with several additional changes to the Miniprofile, USCI (a) represented that clinical testing was not necessary to evaluate the safety or effectiveness of the changes at the same time it allegedly was conducting such testing, and (b) failed to reveal the 1988 design change; and (4) in August 1989, USCI filed a PMA supplement crafted to "legitimize" the 1988 design change. We elaborate briefly on each of these four blocs of evidence.

a. The Change in Manufacturing Location

As previously detailed, the first catheter in the Miniprofile line was called the "Simplus." Until the end of 1987, USCI manufactured the Simplus at a plant in Billerica, Massachusetts. In September 1987, USCI acquired a factory building in Haverhill, Massachusetts, and began preparations to move its Simplus manufacturing operations there. The move required approximately six weeks of work from a 25-person crew, structural changes to the buildings, and the installation of filters and purifiers to de-ionize the air and water. The idea was essentially to "replicate" the Billerica Simplus

manufacturing operations, although only some Billerica machines and workers were transferred to the new plant.

On December 15, 1987, USCI filed a PMA supplement requesting FDA approval to manufacture the Simplus at its Haverhill facility. On March 3, 1988, the FDA sent inspectors to the Haverhill plant. After a five-day inspection, the inspectors identified a number of problems with various pieces of equipment at the new plant. On March 23, 1988, Cvinar wrote to the FDA and promised to correct the problems. On June 7, 1988, the FDA approved the PMA supplement for the Haverhill facility, stating in a cover letter that "[y]ou may begin marketing of the device manufactured at this facility upon receipt of this letter." But by that time, USCI already had marketed several thousand catheters manufactured at the Haverhill plant.

As noted above, the regulations for Class III medical devices require the filing of a PMA supplement when an approved device is manufactured at "a different facility and establishment" and the change in location affects the device's safety or effectiveness. See 21 C.F.R. § 814.39(a)(3). The government takes the position that the move from Billerica to Haverhill was one that affected safety or effectiveness and thus required FDA approval prior to the marketing of any catheters

assembled in Haverhill. Defendants respond that, because the Haverhill operations were designed to replicate the Billerica operations, the move was "safety neutral" and the PMA supplement USCI filed was in fact unnecessary. Defendants also contest the sufficiency of the evidence linking them with the decision to market Haverhill-manufactured catheters prior to FDA approval.

b. The 1988 Design Change

On May 24, 1988, the FDA approved the marketing of the Miniprofile catheter, which evolved from the Simplus. As approved, the Miniprofile contained three "lumens," which are the tiny tubes used to inflate and deflate the balloon. Originally, USCI intended to manufacture the Miniprofile with a "fast purge" system that facilitated quick elimination of air from the lumens prior to filling them with the liquid that would inflate the balloon. The fast purge system was patented, however, and USCI ultimately could not use it in the Miniprofile.

Following its commercialization, the Miniprofile developed a reputation for having a deflation problem. There was evidence that the problem was largely traceable to end users not preparing and purging the catheter in accordance with the

instructions in its labeling. But there also was evidence that the round shape of the Miniprofile's lumens may have been a contributing factor. In any event, the perception that the Miniprofile had a deflation problem affected sales, and USCI began investigating the possibility of an ameliorative modification.

Eventually, USCI decided that a reduction in the number of lumens from three to two would positively affect Miniprofile deflation issues. The company created a two-lumen prototype and, after bench testing, shipped it for investigational use in humans. USCI did not secure an IDE prior to its investigation of the device, the objective of which (as stated in an internal USCI document) was "[t]o evaluate the 2 Lumen Mini/Simplus catheter for improved inflation/deflation times; and to verify that non-deflation of the balloon will not occur." On November 3, 1988, a USCI employee sent the Management Board and Breakfast Club a memorandum summarizing the results of the company's testing. On November 7, 1988, Cvinar informed Prigmore in writing that testing of the two-lumen Miniprofile had been completed, that the testing revealed "significantly better inflation/deflation times with latest 2 lumen version," and that USCI would be changing to the two-lumen design "post haste." On November 17, 1988, Cvinar sent the Management Board

a memo explaining that the changeover to a two-lumen Miniprofile was a "safety issue" and linking the decision with the need to "remain competitive in key market areas."

USCI did not file a PMA supplement prior to marketing the two-lumen Miniprofile. Moreover, the company took steps that tend to evince an intent to conceal the change from the FDA. For example, Leichter would not permit USCI's vice president of marketing to issue a brochure with a diagram of the modified catheter because the diagram was "inconsistent with what had been submitted to the FDA . . . ." Leichter also rejected a subordinate's suggestion that the label of the modified device reflect the decreased number of lumens, explaining that "[w]e don't want it to be evident to the FDA, so I would rather have something different that would not be so obvious." Instead, USCI adopted more complicated inventory-sorting and labeling methods. The government takes the now-familiar position that the testing and marketing of the two-lumen Miniprofile violated the Class III medical device regulations because the testing was for purposes of determining the modified device's safety or effectiveness yet was performed without an IDE, see 21 C.F.R. Part 812, and because the change from three to two lumens affected the device's safety or effectiveness yet was implemented without a PMA supplement, see

id. § 814.39(a). Here again, Prigmore asserts evidentiary insufficiency and all defendants contend that, under their understanding of the regulations, neither an IDE nor a PMA supplement was required in connection with the testing and marketing of the two-lumen Miniprofile.

c. The 1989 PMA Supplements

Throughout 1989, USCI modified the Miniprofile by creating versions of the device with (1) a silicone coating, (2) a balloon bond cured by ultraviolet light, (3) longer and thicker balloons, and (4) a thinner shaft (the so-called "Solo" model). USCI filed PMA supplements for these modifications, asserting that clinical testing was not required to verify the continued safety and effectiveness of the device. In fact, however, USCI investigated how each of these models performed in humans without having secured an IDE from the FDA. The plans for and results of these tests were documented in various memoranda sent to Leichter and Cvinar. In addition, with the exception of the Solo submission (which in one section mentioned that the device had two lumens), the PMA supplements for these modifications did not reveal that the Miniprofile was, by 1989, a two-lumen catheter. This apparently was not an accident. There was evidence that Leichter directed that a draft of the PMA supplement for the Miniprofile with the new balloon sizes be

altered to remove a passage describing the catheter as having two lumens because "right now it wasn't a good time" to mention the change in light of "what had happened with the Probe."

Defendants' response to the government's argument that this evidence suggests a conspiracy to defraud is basically the same as that with respect to the three-to-two lumen change. Prigmore asserts that there is insufficient evidence that he knew or approved of these events. The other defendants do not disclaim the necessary knowledge and approval. Rather, they assert that the "testing" of these modifications without an IDE and the failure to reveal the three-to-two lumen change were not unlawful given their understanding of the regulatory requirements.

d. The "Legitimizing" 1989 PMA Supplement

In August 1989, USCI allegedly conceived a plan to obtain post hoc FDA approval of the two-lumen Miniprofile. The company decided to file a PMA supplement for a new catheter in the Miniprofile line called the "Solo Sr." The supplement would disclose and seek approval for the three-to-two lumen change as if it were not already a done deed. As explained in a memorandum summarizing an August 30, 1989 Regulatory Affairs Meeting attended by Leichter and Prigmore, USCI would "'legitimize' the changes [it] ha[d] already made (3 lumen to 2

. . .)" by submitting a PMA supplement "within a month." Leichter told a subordinate that the Solo Sr. PMA supplement was designed as a "cleanup" filing to secure FDA approval of a product already being shipped. As noted previously, the PMA supplement submitted for the Solo Sr. was eventually withdrawn.

During the late summer of 1989, Leichter walked into a Management Board meeting carrying a group of files on the Miniprofile line and announced that the files were problematic and "not clean." William Longfield, the Chief Operating Officer of Bard, replied by asking whether the records could be "purged." In response, Cvinar halted the meeting and sent the participants out of the room. After a break, the meeting resumed and the subject of purging the files did not arise again.

Despite his presence at the meeting where it was decided that USCI would attempt to “legitimize” already-made changes to the Miniprofile, Prigmore again argues that there is insufficient evidence to prove that he knew of or condoned USCI's actions with respect to the Solo Sr. The other defendants contend that the Solo Sr. was not in fact the then-extant Miniprofile, pointing to evidence that the device was to have a blood-pressure monitoring capability not then present in the Miniprofile. In other words, defendants take the position

that the Solo Sr. PMA supplement was not fraudulently filed in an attempt to legitimize already made changes to the Miniprofile; rather, it was filed "in order to seek approval of changes and features other than the number of lumens." Defendants additionally contend that the Solo Sr. PMA supplement was filed at the direction and under the supervision of David Thomas, USCI's Vice President of Regulatory Affairs and an immunized government witness.

C. Relevant Procedural History

As indicated above, the primary defense theme at trial was that, under defendants' understanding of the applicable statutory and regulatory requirements, the testing and marketing efforts at the root of the charged conspiracy were not fraudulent. This theme had two components pressed by defendants in the alternative: (1) defendants' understanding of the legal requirements was correct; or (2) defendants' understanding of the legal requirements, even if incorrect, was objectively reasonable and therefore foreclosed a fraud prosecution based on a stricter reading of the law. See, e.g., United States v. Rowe, 144 F.3d 15, 21-23 (1st Cir. 1998) (applying the rule that, in a fraud prosecution premised on an alleged violation of ambiguous positive law, the defendant is entitled to have his culpability assessed against the interpretation of the law that

most tends to rebut the charge of intentional deceit so long as the interpretation is objectively reasonable).

Although defendants took a number of different legal positions based on the specific language of the pertinent regulations, the foundation supporting their primary defense theme tracked USCI's earlier argument, set forth in the May 15, 1989 letter to the FDA, that a Class III medical device manufacturer is only required to file a PMA supplement when it modifies an approved device and the modification affects the device's safety or effectiveness when the device is used in accordance with its "intended conditions of use" – i.e., the conditions of use prescribed in the labeling. Thus, the argument ran, modifications affecting the device's safety or effectiveness only during "unlabeled," and thus unintended, conditions of use, such as overrotation with respect to the Probe line and improper preparation and purging with respect to the Miniprofile line, did not affect the device's safety or effectiveness within the meaning of the applicable regulations.

In support of their argument, defendants relied heavily upon 21 U.S.C. § 360c(a)(2) and 21 C.F.R. § 860.7, which by their terms define for the FDA when a device is to be regarded as safe and effective. These provisions combine to suggest that

the safety and effectiveness of a device are to be determined by, inter alia, weighing its benefits to health against the probable risks from use of the device for its intended conditions of use. See id. In a nutshell, defendants' position was that, if the FDA determines a device's safety and effectiveness within the context of the device's intended conditions of use, it was at least reasonable for them to assume that modifications which affect a device's safety or effectiveness only during unintended conditions of use do not affect "safety" or "effectiveness" within the meaning the applicable law.[1]

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[1]As to the claim that the clinical testing described above violated 21 C.F.R. Part 812 because it was done without an IDE "to determine [the] safety and effectiveness" of the various device modifications, § 812.2(a), defendants in part relied on a derivative of their argument responding to the government's claims of illegal marketing. With respect to modifications for which, in defendants' view, no PMA supplement was required, defendants reasonably understood that an IDE also was not required because an IDE is nothing more than an "exemption permit[ting] a device that otherwise would be required . . . to have premarket approval to be shipped lawfully," id. § 812.1(a). With respect to the preapproval testing conducted on modified devices for which a PMA supplement admittedly was required (e.g., Probe B), defendants asserted that they regarded the testing to be consumer preference testing exempted from the IDE requirements by § 812.2(c)(4).

In their submissions to this court, defendants also hint at an all-encompassing argument that they reasonably did not regard any of the allegedly unlawful clinical "testing" charged by the government to violate Part 812. According to this argument, as we understand it, defendants reasonably read Part 812 as merely prescribing the protocols for the gathering of the "valid scientific evidence" upon which the FDA will assess the safety

The government did not agree with defendants' asserted understanding of the crucial statutory and regulatory provisions, or with defendants' alternative argument that, even if not correct, defendants' understanding was objectively reasonable and therefore the appropriate benchmark against which criminal liability should be judged. Rather, the government took the position that any modification known by the manufacturer to affect the safety or effectiveness of an approved Class III device – even a modification only affecting safety or effectiveness during unlabeled and warned-against conditions of use – triggers the obligation to file a PMA supplement. The government supported this so-called "plain" or "dictionary" meaning of the phrase "affecting the safety or effectiveness of the device" in 21 C.F.R. § 814.39(a) with the testimony of two FDA experts and a Bard executive, all of whom

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and effectiveness of new and modified devices pursuant to § 860.7(d)(1) and (e)(1). The testing at issue in this case was not for purposes of gathering this type of "valid scientific evidence"; it was more in the way of informal feedback gathered on the front lines by USCI sales representatives and passed back to corporate headquarters. Thus, the argument concludes, while the prior shipment of the catheters in question might have violated § 814.39(a), their actual use in humans did not independently violate Part 812.

Whatever merits this alternative argument might have, we disregard it for present purposes because defendants did not sufficiently develop and preserve it as a defense theory in the district court. See United States v. Zannino, 895 F.2d 1, 17 (1st Cir. 1990).

shared with the jury their understandings of the crucial Class III medical device regulations. Although the experts gave testimony that generally tended to support the government's case, defendants were able to elicit on cross-examination of the FDA witnesses that a manufacturer attempting to divine the meaning of the phrase "affecting the safety or effectiveness of the device" reasonably might cross-reference § 860.7, and that this regulation does indeed circumscribe the concepts of "safety" and "effectiveness" in terms of "intended . . . conditions of use."

Consistent with their position on the meaning of the phrase "affecting the safety or effectiveness of the device," defendants requested that the district court instruct the jury to construe the phrase in the light cast by 21 C.F.R. § 860.7. Accordingly, defendants asked the court to quote § 860.7(d)(1) and (e)(1) verbatim and to instruct the jury to "seek the definition[s] of 'safe' and 'effective'" in these provisions. Defendants further asked that the court instruct the jury "to determine the safety and effectiveness of a device or of a change to a device, not under any conditions of use, but in light of the conditions of use, directions for use, and warnings against unsafe use contained in the manufacturer's labeling for that device." Finally, defendants asked the court to instruct

the jury that "the defendants' interpretation of the standard they were to use in determining safety and effectiveness was reasonable."

The government, by contrast, opposed defendants' attempt to link 21 C.F.R. § 860.7 to the phrase "affecting the safety or effectiveness of the device" in § 814.39(a). The government argued that § 860.7 is intended only to guide the FDA as to whether a device is safe and/or effective; it is not intended to advise the manufacturers of Class III medical devices in connection with their PMA supplement filing obligations. Accordingly, the government asked that, in instructing the jury, the district court (1) simply quote the relevant portions of § 814.39 (but not § 860.7); (2) define the terms "safety" and "effectiveness" according to "their plain ordinary meaning," – i.e., "freedom from danger or risks" and "having a definite or desired effect," respectively; and (3) state that there is no exemption from the relevant filing requirements "based upon a misuse of the device by users of the device," and that "a PMA supplement must be filed . . . for a change that affects safety and efficacy regardless of the reason for the change" – i.e., even if the change affects safety or effectiveness of the device only in the event of unlabeled or warned-against conditions of use.

The district court did not adopt either approach. Instead, the court advised counsel on the day before closing arguments that, although it would permit defendants and the government to argue to the jury their respective interpretations of the applicable Class III medical device statute and regulations, it would only instruct on conspiracy to defraud. The court thus would not instruct on either the meaning of the underlying statute and regulations or objectively reasonable interpretations thereof.

Accordingly, counsel for Leichter and Cvinar stressed in their closing arguments that, as the relevant statute and regulations were reasonably understood by their clients, a modification to an approved Class III medical device affected the device's safety or effectiveness (and triggered the PMA supplement filing requirement) only when the modification impacted safety or effectiveness during the device's intended conditions of use. Counsel for Leichter and Cvinar also emphasized that the intended conditions of use were to be found in the device's labeling instructions and warnings. Counsel for Prigmore primarily focused on whether there was sufficient evidence to tie his client to the conspiracy, but also joined in Leichter and Cvinar's legal arguments to the district court. The government, for its part, prominently argued that "safety"

and "effectiveness" should be given their plain or dictionary meanings, and that modifications affecting safety or effectiveness during unlabeled or warned-against uses were subject to the regulatory filing requirements. The government also suggested that 21 C.F.R. § 860.7 is intended only to guide the FDA in making its safety and effectiveness assessments, and has no bearing on a manufacturer's obligation to file a PMA supplement.

Subsequently, as promised, the district court declined to instruct the jury on the meaning of the statute and regulations. Rather, the court instructed on the elements of conspiracy to defraud, and specified that defendants were accused of conspiring to defraud the FDA in three respects: (1) "knowingly and willfully, and with an intent to defraud, failing to submit applications for product approval and testing [to] the FDA, which allegedly they were required to submit"; (2) "concealing or failing to report material facts which allegedly they were required to report"; and (3) "making false statements in documents that they submitted to the FDA."

The district court also gave detailed state-of-mind instructions, emphasizing that the government was required to prove beyond a reasonable doubt that defendants had knowledge of their legal duties (on this point, the court simply provided the

jury with copies of the applicable Class III medical device statutory and regulatory provisions); that defendants specifically intended to agree to violate these duties and thus defraud the FDA; and that defendants "did not act in good faith or by mistake, accident, or neglect." Defendants timely objected to the court's refusal to instruct that the terms "safety" and "effectiveness" in the provisions spelling out defendants' legal duties must be understood as described and confined by 21 C.F.R. § 860.7 and, alternatively, to the court's refusal to instruct that defendants' interpretation of the regulatory requirements was at the very least reasonable. On the sixth day of its deliberations, the jury convicted defendants. These appeals eventually ensued.

II.

As we stated at the outset, defendants raise a number of issues. All three defendants press various arguments that the underlying convictions should be reversed and the conspiracy charge dismissed. All three defendants also assert a number of alternative arguments that their convictions should be vacated and the matter remanded for further proceedings. Prigmore additionally contends, again in the alternative, that his sentence was unlawful. In the end, we are not persuaded by defendants' arguments for reversal and dismissal. Yet we are convinced that the convictions should be vacated and the case remanded for further proceedings. To simplify our analysis, we shall begin by explaining why vacatur is warranted and then proceed to explain why reversal and dismissal is not. We do not reach the merits of any arguments for vacatur beyond the one we regard as dispositive because, in any retrial, the issues giving rise to these other arguments are either not likely to arise again or likely to arise in materially different contexts. For the same reason, we do not address the merits of Prigmore's sentencing challenge.

A. The Dispositive Issue

Defendants contend, inter alia, that the district court committed reversible error in refusing to instruct the jury that

defendants' asserted understanding of when a change should be regarded as "affecting the safety or effectiveness" of a Class III medical device, and thus trigger the PMA supplement filing requirement, was at least reasonable and therefore the measure against which defendants' criminal culpability should be assessed. In defendants' view, the trial record and the logic of the rule we applied in Rowe, see 144 F.3d at 21-23, entitled them to such an instruction as a matter of law. We do not believe that the court was obliged to discuss the concept of reasonableness in its instructions; an instruction that the jury should simply apply a definition of the applicable phrase informed by the limitations of 21 C.F.R. § 860.7 and tailored to the evidence in this case would have covered the point just as well. Nonetheless, on the facts of this case, we agree that the court erred in not instructing the jury to determine defendants' guilt against the backdrop of such a definition.

We begin by acknowledging that the district court has considerable discretion in how it formulates, structures, and words its jury instructions. See, e.g., United States v. Woodward, 149 F.3d 46, 68 n.14 (1st Cir. 1998). Moreover, the court often acts within its discretion in refusing to elaborate the meaning of even an important legal term or phrase that falls short of being self-explanatory. Indeed, we have recognized

that, in some instances, attempts to clarify inherently nebulous concepts can do more harm than good. Cf. United States v. Andujar, 49 F.3d 16, 23 (1st Cir. 1995) (explaining our repeated warnings that district courts within this circuit should avoid defining the phrase "reasonable doubt" in their jury instructions). The applicable standard, informed in part by these principles, is that a court's refusal to give a requested instruction is reversible error only if the requested instruction was (1) substantively correct; (2) not substantially covered elsewhere in the charge; and (3) concerned a sufficiently important point that the failure to give it seriously impaired the defendant's ability to present his or her defense. See, e.g., United States v. Rose, 104 F.3d 1408, 1416 (1st Cir. 1997). In our view, this is the relatively rare case where all three of these requirements are met.

As an initial matter, defendants are plainly correct in asserting that, under settled circuit law, they were entitled to have their intent assessed in the light of the interpretation of the underlying filing requirements that is most congenial to their case theory and yet also objectively reasonable. See Rowe, 144 F.3d at 21-23 (bankruptcy fraud case) (applying this principle to hold that an allegedly false statement was not fraudulent because it was not in fact false under an objectively

reasonable interpretation of the underlying disclosure requirement); United States v. Migliaccio, 34 F.3d 1517, 1525 (10th Cir. 1994) (applying the rule in a mail fraud prosecution); cf. United States v. Bradstreet, 135 F.3d 46, 52 (1st Cir. 1998) (securities fraud case) (endorsing such a rule in dicta). This rule, rooted in the due process-based "fair warning requirement," see United States v. Lanier, 520 U.S. 259, 265-67 (1997), recognizes that, in a prosecution based on the theory that a defendant has defrauded the government by making false statements in information defendant was duty-bound to divulge to the government (or by failing to divulge information defendant was duty-bound to divulge), there has been no crime if the statements were not false (or if there was no duty to divulge) under an objectively reasonable interpretation of the law imposing the duty. See Rowe, 144 F.3d at 21. The government does not take issue with this general principle; in fact, it makes no mention at all of Rowe or Bradstreet despite defendants' significant reliance on them.

We also think it apparent that, if the evidence at trial gives rise to a genuine and material dispute as to the reasonableness of a defendant's asserted understanding of applicable law, the judge, and not the jury, must resolve the dispute. See United States v. Cheek, 498 U.S. 192, 203 (1991)

(tax fraud case) (observing that the objective reasonableness of defendant's view of the law is a legal question); Rowe, 144 F.3d at 21-23 (treating the reasonableness question raised in that case as a matter of law).[2] On this general point, the government's agreement is explicit.

Indeed, despite its position at trial, the government no longer affirmatively takes issue with the general proposition that it was reasonable for defendants to have regarded the definition of the phrase "affecting the safety or effectiveness of the device" in 21 C.F.R. § 814.39(a) as properly informed by

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[2]To be sure, a reasonableness determination sometimes requires preliminary resolution of underlying factual disputes, and the court almost certainly acts within its rights in asking the jury to resolve these disputes. Cf. Bradstreet, 135 F.3d at 50-52 (suggesting in dicta that, had there been a genuine dispute as to which of several "revenue recognition policies" defendant had been "booking" revenue under, and had an allegedly fraudulent booking of revenue been appropriate under an objectively reasonable interpretation of one such policy, then the court would have been obliged to instruct the jury to assess culpability in the light of that reasonable interpretation so long as it first found defendant to have been using that policy in booking the revenue in question); St. Hilaire v. City of Laconia, 71 F.3d 20, 24 n.1 (1st Cir. 1995) (civil rights damages action) (observing in a discussion of the qualified immunity defense and its "objective reasonableness" criterion that it is an open question whether the judge may decide underlying factual disputes bearing on reasonableness or must ask the jury to resolve such disputes). But as a legal question, the reasonableness of defendants' understanding is ultimately a question for the judge. See Nieves-Villanueva v. Soto-Rivera, 133 F.3d 92, 99 (1st Cir. 1997) (noting that, in our legal system, purely legal questions are exclusively within the domain of the judge).

the context-providing qualifications set forth in § 860.7. Although at oral argument the government declined to disavow the "plain meaning" or "dictionary" definitions of the terms "safety" and "effectiveness" that it pressed at trial and in its closing arguments, the government makes no real effort to defend those definitions in its brief to this court. Perhaps this is because the Supreme Court recently recognized that "virtually every drug or device poses dangers under certain conditions," FDA v. Brown & Williamson Tobacco Corp., 120 S. Ct. 1291, 1305 (2000), and repeatedly emphasized that a drug or device is safe within the meaning of the FDCA when, in connection with its intended uses and conditions of use, see generally id. at 1301-06, its "therapeutic benefits outweigh the risk of harm," id. at 1305. Perhaps this is because, on cross-examination, the FDA experts who testified concerning the meaning of the applicable regulations conceded that it was reasonable to refer to the phrase "intended . . . conditions of use" in § 860.7(d)(1) and (e)(1) in ascertaining the meaning of the phrase "affecting the safety or effectiveness of the device" in § 814.39(a).[3] Perhaps

[3]In referring to the experts' testimony regarding the meaning of the applicable laws, we do not wish to be understood as more generally endorsing the use of expert testimony on legal meaning. Neither side contests the appropriateness of the expert testimony that took place in this case, so we do not address its admissibility. We feel it important to note, however, that expert testimony proffered solely to establish the

the government has simply changed its position because it now agrees with defendants' argument that terms and phrases repeated throughout a given law generally carry the same meaning. See, e.g., United States v. Nippon Paper Indus. Co., Ltd., 109 F.3d 1, 4-5 (1st Cir. 1997). In any event, to the extent that the government may have tacitly conceded the general point, we regard the concession as proper. For the reasons just stated, and regardless how the phrase "affecting the safety or effectiveness of the device" in § 814.39(a) ultimately ought to be understood, it was objectively reasonable for defendants to regard the phrase as definitionally circumscribed by the "intended . . . conditions of use" qualification found in, among other places, § 860.7(d)(1) and (e)(1).

That said, the government does not concede that the district court committed reversible error in declining to give the instruction defendants requested. Put in the language of the three-part test under which we review the court's refusal to instruct, see Rose, 104 F.3d at 1416, the government's argument,

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meaning of a law is presumptively improper. See Nieves-Villanueva v. Soto-Rivera, 133 F.3d at 99-101; see also Benjamin J. Vernia, Annotation, Admissibility of Expert Testimony Regarding Questions of Domestic Law, 66 A.L.R. 5th 135 (1999) (detailing how, despite the inroads courts have made into the rule against expert testimony on questions of law, such testimony is still usually excluded).

in essence, is that there has been no error because the instruction defendants requested was neither substantively correct nor concerned a sufficiently important point that the court's failure to give it seriously impaired defendants' ability to present their defense, see id.[4] We disagree.

As to the first Rose factor, substantive correctness, the government points out that defendants requested that the court instruct the jury not only that it should link the phrase "affecting the safety or effectiveness of the device" in 21 C.F.R. § 814.39(a) with the phrase "intended . . . conditions of use" in § 860.7(d)(1) and (e)(1), but that it also should understand "intended . . . conditions of use" in terms of the device's labeling. Such a definition was too narrow, according to the government, because there was evidence that, with respect to Probe B, defendants knew of and acquiesced in USCI's on-the-side promotion of the overrotation against which the device's label warned. As the government sees it, all actual conditions of use that the manufacturer intends or even knows of are relevant to the safety-or-effectiveness inquiry, and modifications affecting a device's safety or effectiveness

[4]It is undisputed that the instruction defendants requested was not substantially covered elsewhere in the charge. See Rose, 104 F.3d at 1416. Thus, we address only the first and third prongs of the Rose standard.

during such conditions of use trigger the PMA supplement-filing requirements even if they are specifically warned against on the label. In making this argument, the government points out that § 860.7(b)(2) specifies that "[t]he conditions of use for [a] device[] includ[e] conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use." (emphasis supplied).[5]

Given the explicit references to intention in 21 C.F.R. § 860.7(d)(1) and (e)(1), and in the absence of some clarifying regulatory or judicial gloss to support the government's position, see Lanier, 520 U.S. at 266 (recognizing that "uncertain" laws can be clarified by authoritative construction), we are not persuaded that a criminal fraud

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[5]The government also draws support for this argument from 21 C.F.R. § 801.4, which was neither the subject of trial argument nor given to the jury. In relevant part, § 801.4 states:

> The words "intended uses" or words of similar import in [three regulations not relevant to this case] refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. The objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised . . . .

prosecution can be premised upon a failure to file a PMA supplement in connection with a modification to an approved device that affects the device's safety or effectiveness only with respect to a sincerely unintended and warned-against, albeit known, condition of use.[6] Yet we think that the regulatory text does accommodate the government's argument that a manufacturer must take into account unlabeled, though promoted (and thus “intended”), conditions of use in determining whether a modification affects safety or effectiveness. Moreover, given the evidence of USCI's promotion of Probe B overrotation, such a jury instruction might well be necessary at any retrial if there is sufficient evidence that defendants knew of or acquiesced to such promotion.

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[6]We of course recognize that, if a modification makes an approved device more dangerous in the event of a condition of use that sometimes occurs despite the manufacturer's best efforts to prevent it, there may be sound policy reasons for requiring the manufacturer to file a PMA supplement. But we are concerned here not with the most socially useful interpretation of the relevant regulations; we are concerned with whether those regulations gave fair warning that a failure to file a PMA supplement in such a circumstance is a felony under federal law. See Lanier, 520 U.S. at 265-67. Because the most relevant regulation defines device safety in terms of "intended . . . conditions of use," § 860(d)(1) (emphasis supplied), and because there has been no authoritative judicial or regulatory pronouncement clarifying that a sincerely warned-against but known condition of use should be regarded as "intended," see Lanier, 520 U.S. at 266, we reject the government's argument on this narrow point.

But under the circumstances of this case, we do not think it appropriate to hold that the defendants' reference to labeling in their requested instruction effectively waived their right to an instruction that, for purposes of this prosecution, the "intended . . . conditions of use" qualification in 21 C.F.R. § 860.7(d)(1) and (e)(1) limits the meaning of the phrase "affecting safety or effectiveness" in § 814.39(a). Although defendants' proposed instruction did request that the jury be instructed in terms of labeling, it more generally requested (over the government's objection) that the jury be instructed in the specific language of § 860.7(d)(1) and (e)(1), both of which state broadly, without specific reference to labeling, that "intended . . . conditions of use" are relevant to safety and effectiveness determinations. In other words, but for a proposed refinement suggesting that the label instructions reveal the manufacturer's intended conditions of use (as in most cases they would), defendants' request was sufficiently close to the mark. Moreover, and more to the point, we think it evident that the government's promotion at trial of an overly broad (at least for purposes of assessing criminal liability) definition of the relevant statutory and regulatory terms had as much, if not more, to do with this issue not emerging in sharp relief as did any lapse on defendants' part. Defendants' requested

instruction was thus adequate to preserve the issue. Cf. United States v. Sanborn, 563 F.2d 488, 490-91 (1st Cir. 1977) (vacating a conviction on the basis of a rule of law slightly different, and less defendant-friendly, than that sought by the defendant in his requested instruction).

As to the third Rose factor, whether the requested instruction concerned a sufficiently important point that the district court's failure to give it seriously impaired defendants' ability to present their defense, the government appears to make two arguments. First, the government makes a halfhearted claim that the court's good-faith instructions "adequately articulated" the no-mens-rea defense theory and thus rendered unimportant the court's failure to define the disputed underlying regulatory requirements. See Gov't Br. at 111. We disagree. While the court's good-faith instructions were comprehensive, articulate, and beyond reproach insofar as they generally described the concept of good faith, the jury's good-faith finding may well have been affected by its view of what the underlying law required. The trial evidence, closing arguments, and the jury instructions might well have left the jury with an erroneous belief that manufacturers face criminal liability for failing to file a PMA supplement when they make a modification to an approved device that has an effect only

during a sincerely unintended and specifically warned-against condition of use. This erroneous belief, in turn, might well have been the basis upon which the jury rejected the good-faith defense. The good-faith instruction thus did not undo the harm caused by the court's failure to give the requested instruction in and of itself. See Migliaccio, 34 F.3d at 1525.

Second, the government in substance contends that, even if erroneous, the district court's failure to define the underlying regulatory terms was unimportant because it was harmless beyond a reasonable doubt within the meaning of Neder v. United States, 527 U.S. 1, 16-20 (1999) (holding harmless the trial court's erroneous failure to instruct the jury to determine whether a failure to report taxable income was "material" where the failure to report involved over $5 million, the evidence regarding the failure to report was not controverted, and defendant did not argue to the jury that his failure to report was immaterial). The government suggests that, as in Neder, it is here "clear beyond a reasonable doubt that a rational jury would have found" defendants guilty even if properly instructed. Id. at 18 (emphasis supplied).[7]

[7]In arguing that any error here was harmless "beyond a reasonable doubt," the government appears to take the position that instructional error of the type we have identified is constitutional in dimension. See Chapman v. California, 386 U.S. 18, 24 (1967) (holding that, "before a federal

Indeed, in the government's view, "[t]his case . . . presents a stronger candidate for a finding of harmlessness" than did Neder because the legal error in Neder affected the jury's consideration with respect to all of defendant's allegedly illegal acts. Gov't Br. at 80. In contrast to Neder, the government asserts, the error in this case only affected the jury's deliberations with respect to those acts pertaining to the failure to obtain a PMA supplement; the error did not affect the jury's consideration of the evidence of the testing violations, the evidence that defendants failed to disclose the three-to-two lumen change in the 1989 Miniprofile PMA supplements, the evidence regarding deceptive intentions with respect to the filing of the Solo Sr. PMA supplement, the

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constitutional error can be held harmless, the court must be able to declare a belief that it was harmless beyond a reasonable doubt"). One member of the panel, however, believes that the error likely was not constitutional, and that the applicable harmless-error standard therefore comes from Kotteakos v. United States, 328 U.S. 750, 776 (1946) (interpreting the predecessor to the federal harmless-error statute, 28 U.S.C. § 2111, to require reversal only when the error "had substantial and injurious effect or influence in determining the jury's verdict"). See Brecht v. Abrahamson, 507 U.S. 619, 630-32 (1993) (noting that the Chapman standard applies to direct review of constitutional errors and that the Kotteakos standard applies to direct review of non-constitutional errors). Because the panel unanimously agrees that the error we discern cannot be said to be harmless under either test, we do not decide which test applies or, concomitantly, whether the error deprived defendants of a constitutional right.

evidence of USCI's failure to report modifications in mandatory follow-up reports, or the evidence of other assorted deceit and trickery (e.g., promoting Probe B contrary to its label warnings and adopting complicated inventory and labeling methods designed to conceal device modifications from the FDA). And, the argument concludes, the evidence with respect to these matters was "overwhelming." Id.

In our view, the evidence of guilt in this case is quite substantial; certainly, it is more than sufficient to permit a retrial on a properly formulated theory that defendants conspired to defraud the FDA with respect to its oversight and regulation of medical devices. We do not believe, however, that the evidence is so one-sided as to render harmless the underlying instructional error we have identified. Unlike the government, we do not see this as a case, like Neder, where it is far-fetched to conclude that a properly instructed jury might have returned different verdicts than those returned. In explaining, we follow the government's lead and focus upon the nature and weight of the evidence asserted to have been unaffected by the instructional defect.

The government first asserts that the trial evidence showed conclusively that defendants tested their device modifications for the purpose of determining safety and

effectiveness with respect to intended conditions of use and in such a way as to put patients at prohibited risks. In responding to this argument, we limit ourselves to the factual nature of the evidence presented and put to the side defendants' legal argument that, because an IDE is an exemption permitting the clinical testing of unapproved devices that otherwise could not lawfully be shipped without premarket approval, the lawfulness of most of the testing at issue in this case turns in the first place on whether the modification at issue was subject to the PMA supplement requirement. See supra note 1.

As to the nature of the testing evidence, we think that, while the factual inference the government would have us draw surely would be permissible on the present record, see, e.g., supra at 13, 20, 23-24 (summarizing documentary evidence suggesting that the testing was for purposes of evaluating safety and/or efficacy during intended conditions of use), it is not the only rational inference. Unlike Neder, the government's evidence as to the purpose of the testing was contested by defendants; as we have stated, defendants introduced testimonial evidence that the purposes of this testing were to determine whether the modifications were ameliorating safety concerns during unintended conditions of use and/or to establish consumer preferences within the meaning of 21 C.F.R. § 812(c)(4). See

supra at 13-14. Given Neder's repeated emphasis on the "uncontested" nature of the evidence of materiality in that case, see 527 U.S. at 15, 17, 17 n.2, & 19, the contested nature of the testing evidence in this case might well suffice to distinguish it from Neder in and of itself.

In any event, while the government's evidence of the purpose behind the testing was strong, the competing evidence was not inherently incredible. That effectively ends the matter. As an appellate court, we are not equipped to make the credibility determinations that must be made in choosing between these clashing blocs of evidence, each of which is sufficient to render rational a finding in favor of its proponent. See Neder, 527 U.S. at 19. We also are mindful that, in denying defendants' motions for judgments of acquittal, the trial court thought it a very "close" call whether the motions should be granted, and that, in overruling defendants' objections to its failure to give the requested safety-and-efficacy instruction, the court opined that instructing the jury as the defendants requested would be tantamount to directing a verdict for them. In sum, we do not regard the government's evidence of the purpose of the testing, alone or combination with the other

evidence discussed below, to be of such a nature as to render the court's instructional error harmless.

Our analysis with respect to the other evidence mentioned by the government in support of its harmless-error argument follows a similar path. As we have observed, defendants explained the failure to file a PMA supplement with respect to the three-to-two lumen change in the Miniprofile with evidence and argument that a filing was unnecessary because the change was designed to ameliorate safety issues caused by unintended preparation and purging techniques by end users. See supra at 23. The evidence on this point was not inherently incredible. If a correctly instructed jury were to have accepted this evidence and line of defense (as it might have), we think it might well also have regarded the subsequent failure to report the three-to-two lumen change in the 1989 Miniprofile PMA supplements as inconsequential. So too with the Solo Sr.; we think it possible that the jury might have accepted defendants' supported and argued contention that USCI filed the Solo Sr. PMA supplement in order to seek approval of changes other than those pertaining to lumen number and/or at the direction and under the supervision of David Thomas, and not defendants.

Finally, with respect to the evidence of failure to submit follow-up reports and the evidence of other assorted deceptions and trickery, it suffices to note that such evidence was either largely tangential to the primary trial themes or not particularly probative of any of the principal fraud theories as to which the jury was instructed. See supra at 34. As we have explained, instructional error and the absence of one-sided and overwhelming evidence of guilt combine to prevent us from affirming defendants' convictions on the basis of the primary criminal liability theories advanced at trial: fraudulent marketing and fraudulent testing. Moreover, the experienced trial judge who presided over the case stated on the record that he was not sure he was correct in even sending the case to the jury. Given this state of affairs, it would be improper to affirm defendants' convictions on the basis of evidence that, on the whole, played a supporting rather than a starring role at trial.

B. Other Issues

As noted, defendants press various arguments for reversal and dismissal of the conspiracy charge. These arguments do not merit extended discussion.

First, all three defendants argued in their initial briefs that the regulations under which they were prosecuted did

not give fair warning of the "dictionary" or "plain language" interpretation that the government relied upon in pressing this prosecution. Then, when defendants perceived in the government's brief a shift in position towards (if not all the way to) the interpretation of the regulations they have advanced all along (and we herein confirm as objectively reasonable), all three defendants suggested in their reply briefs that the conspiracy charge should be dismissed outright because the government's "switch . . . confirms the . . . unconstitutionality of this prosecution." Defendants do not, however, place this argument within the context of a recognized legal theory; nor do they cite authority which supports the drastic remedy they seek. We therefore reject the argument as insufficiently elaborated. See Zannino, 895 F.2d at 17.

Second, defendants Cvinar and Prigmore contend that they are entitled to dismissal of the conspiracy charge because the FDA did not provide them with notice and an opportunity to present to the FDA their "views" as to the events underlying this case prior to reporting their alleged violations of the FDCA to a United States Attorney for prosecution. 21 U.S.C. § 335. But even assuming that Cvinar and Prigmore were entitled to such notice and opportunity, the Supreme Court has made it clear that they are not entitled to dismissal of the

prosecution. See United States v. Dotterweich, 320 U.S. 277, 279 (1943).

Third, and finally, Prigmore asserts that there was insufficient evidence to link him to the conspiracy charged and thus to sustain his conviction. Frankly, in reviewing those portions of the record the government points to in response to Prigmore's sufficiency argument, we are not particularly impressed by the strength of the case against him. Nonetheless, mindful that "in a criminal conspiracy, culpability may be constant even though responsibilities are divided," United States v. Sepulveda, 15 F.3d 1161, 1173 (1st Cir. 1993), and that a successful sufficiency claim requires a showing that "no rational jury could have found [defendant] guilty beyond a reasonable doubt," United States v. Scharon, 187 F.3d 17, 21 (1st Cir. 1999) (emphasis supplied), we are persuaded that there was sufficient evidence to tie Prigmore to the conspiracy.

As we have noted, there was evidence that, on November 7, 1988, Cvinar informed Prigmore that testing of the modified two-lumen Miniprofile had been completed, that the testing revealed "significantly better inflation/deflation times" in the new model, and that USCI would be adopting the two-lumen design "post haste." See supra at 23-24. There thus was evidence to ground a conclusion that Prigmore knew that the three-to-two

lumen change was a change affecting the safety and/or the effectiveness of the Miniprofile – at least with respect to its unintended conditions of use.

Further, there was evidence that Prigmore reviewed for several hours the May 15, 1989 letter in which USCI took the position that the modifications to Probe B that became Probe C did not require a PMA supplement because they did not affect the safety or effectiveness of the catheter during its intended uses and conditions of use. See supra at 18-20. There thus was evidence to ground a conclusion that, by May 1989, Prigmore knew that USCI was under a regulatory obligation to file a PMA supplement with respect to all changes affecting the safety or effectiveness of its approved heart catheters during their intended uses and conditions of use prior to marketing the altered product.

Moreover, there was evidence that, on August 30, 1989, Prigmore participated in the meeting where it was decided that USCI, according to a memorandum memorializing the meeting, would file a PMA supplement for the Solo Sr. designed to "'legitimize' the changes [it] already ha[d] made (3 lumen to 2 . . .)" to the Miniprofile by submitting to the FDA a cleanup PMA supplement. See supra at 26. There is no indication that Prigmore, who then was a Bard vice president with authority over USCI operations,

dissented from the proposed course of conduct, which eventually was implemented. In our view, the memorandum describing the August 30 meeting suggests that Prigmore acquiesced in an unlawful plan to conceal from the FDA a dubious course of conduct, particularly in light of Prigmore's authority, his knowledge of the three-to-two lumen change, and his awareness of the relevant regulatory requirements. This evidence is sufficient to implicate Prigmore in the conspiracy of which he was convicted.

III.

As we have stated, there was substantial evidence that defendants in fact committed the serious crime of which the jury convicted them. But there is too great a possibility that the jury's verdicts were affected by an erroneous failure to define crucial and disputed regulatory terms for us to affirm the convictions under the harmless-error doctrine. We thus vacate defendants' convictions and remand for further proceedings consistent with this opinion.

Vacated and remanded.