CRIMINAL NO. 09-403-03 – 06

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA

v.

MICHAEL D. HUGGINS,
THOMAS B. HIGGINS,
RICHARD E. BOHNER,
JOHN J. WALSH

UNITED STATES' CONSOLIDATED RESPONSE TO DEFENDANTS' OBJECTIONS TO THE PRESENTENCE REPORTS

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The facts outlined in the offense conduct section of the four presentence reports mirror the allegations of the indictment. Those facts are proven by a mountain of documents, including the 81 exhibits attached to the Government's Amended Presentence Memorandum ("G.Mem.") (filed March 30, 2010), as well as the grand jury testimony of a number of witnesses. These facts are beyond any legitimate dispute.

Each of the four defendants signed a plea agreement in which he admitted that, at trial, the government could prove the ultimate facts set out at paragraph 9a through j of the plea agreements. Among other things, each defendant agreed that some person or persons at Synthes had conducted unauthorized clinical testing of the Norian XR bone cement, in violation of the Food, Drug and Cosmetic Act ("FDCA"), by teaching spine surgeons to use that cement in vertebroplasty-type surgeries to treat vertebral compression fractures ("VCFs"), a type of spine fracture often suffered by the elderly. Each defendant admitted further that someone at Synthes promoted Norian XR for use in vertebroplasty-type surgeries to treat VCFs, in violation of the FDCA, notwithstanding that the label warned that XR was "not intended for treatment of

[VCFs]."

Notwithstanding their agreement to the ultimate facts, and despite having received from the government full discovery, each of the defendants continues to dispute the very facts underlying their guilty pleas, as outlined in the Presentence Reports. Their objections fall into four categories: (i) proposed corrections of specific facts; (ii) narrow denials of knowledge of particular events in the chronology; (iii) broad denials of criminal intent; and (iv) philosophical arguments on such topics as whether the government should be permitted to tell the Court about the facts of this case, because each defendant pleaded guilty to a strict liability misdemeanor violation of the FDCA.[1]

The government will review each paragraph of the Presentence Reports to which any defendant has objected by number, addressing each defendant's objections to each numbered paragraph. The offense conduct is contained in ¶¶ 17 through 58 of each Presentence Report. Before addressing these specific objections, however, we respond first to defendant Huggins' general objections that are not addressed to a particular paragraph of the Presentence Report.

A. General Objection – The Park Doctrine (Huggins Objections pages 3 - 4)

Defendant Huggins points out that the responsible corporate officer or Park Doctrine imposes strict liability upon a corporate officer for violations of the Food, Drug and Cosmetic Act ("FDCA"). He suggests that a strict liability criminal offense is "tolerable under the Due Process Clause only because 'penalties are relatively small, and conviction does no grave damage to an offender's reputation,' citing Morissette v. United States, 342 U.S. 246, 256

[1] The four defendants' objections are contained in the Appendix to this filing. Huggins' objections are Exhibit A; Higgins' objections are Exhibit B; Bohner's objections are Exhibit C; and Walsh's objections are Exhibit D.

(1952). Huggins does not mention that the maximum penalty for a misdemeanor violation of the FDCA has always been the same: 12 months in prison. He cites no authority to support his suggestion that liability under the Park Doctrine violates due process, and the government is aware of none. Huggins then continues:

> By entering into the plea agreement, the government avoided the burden of proving any alleged offense conduct to a jury beyond a reasonable doubt. Nevertheless, it has been attempting for nearly two years to use the sentencing proceedings as a forum for asserting that the individual defendants are guilty of participating in a felonious conspiracy to conduct unapproved clinical studies using the Norian product. That approach is simply not what the Supreme Court envisioned when it permitted the RCO doctrine to become law. It is also not consistent with the requirement in the United States Attorney's Manual that the government insist on a guilty plea to "the most serious readily provable charge consistent with the nature and extent of [the defendant's] criminal conduct." See USAM Chapter 9-27-430. Notably, the government never attempted in this case to secure from Mr. Huggins a plea to anything more than a strict liability misdemeanor.

The government is attempting to make the Court aware of all relevant facts and circumstances concerning the offense conduct, as it is obligated to do, and which the Sentencing Guidelines and 18 U.S.C. § 3553(a) require. The government's willingness to agree to a misdemeanor plea agreement with Huggins is in no way inconsistent with this obligation to aprise the Court of the individual facts and circumstances related to each defendant. The maximum penalty for a misdemeanor conviction is 12 months imprisonment. In deciding upon an appropriate sentence within a possible sentencing range of probation to 12 months in prison, the Court can and must take into account the relative individual culpability of each defendant. That is impossible to do without first examining the facts, including the extent of each defendant's actual knowledge of the underlying offense conduct for which each is responsible as a corporate officer and, where applicable, directly participated in such conduct. The Park Doctrine encompasses a wide variety of potentially violative conduct by responsible corporate

officers, ranging from those with no actual knowledge of the underlying criminal violations for which they are ultimately responsible, to those who, as here, participated to some extent in the underlying criminal conduct or otherwise had knowledge of it. Whereas in cases involving the former, a defendant may argue that a sentence of probation is appropriate, in cases such as the present one, the Court can and should consider whether a sentence of imprisonment up to the statutory maximum of 12 months is appropriate.

During the plea negotiations in this case, defendants attempted to persuade the government to agree to a sentence of probation or to otherwise agree not to recommend a term of imprisonment. The government refused to agree to such a provision. Each defendant, including Huggins, understood that a guilty plea in this case could result in a potential maximum sentence of 12 months imprisonment. Each defendant also understood that the government would make the Court aware of all of the relevant facts and circumstances. Contrary to Huggins' claim, the government's charging and plea decisions in this case are in no way inconsistent with the United States Attorney's Manual. To the contrary, the government's charging and plea decisions in this case fully take into account the myriad factors that are described in the USAM, which encompass far more than simply charging the most serious possible offense in every case. The government, exercising its prosecutorial discretion, and in consideration of all of the facts and circumstances, including the offense conduct, the advisory guidelines range, the maximum penalty, the individual circumstances of each defendant, and the fact that the guilty plea agreements resolved the charges against all four individual defendants at the same time and avoided the time, expense and risk of trial, made the decision to proceed with a single misdemeanor charge against each defendant. It stands by that decision. The possibility of more serious felony charges does not, as

Huggins suggests, establish that the government has acted improperly in resolving the case in the manner in which it has chosen to do,[2] and completely ignores that there are a host of other factors that must be considered in making charging and plea decisions.

By pleading guilty, Huggins has limited his maximum exposure to 12 months imprisonment. His effort to deflect the Court's attention away from his own individual culpability to an examination of the government's charging and plea decisions should be turned aside. Each Park Doctrine case must be considered in the context of its individual facts and circumstances. That Congress has decided that a maximum sentence of 12 months' imprisonment for misdemeanor offenders may be appropriate in some cases makes it clear that not every case should result in probation, as defendants suggest, nor should a sentencing court ignore the knowledge and intent of such offenders, as defendants have urged.

B. General Objection – The Norian Product Labels (Huggins Objections pages 7 - 9)

Huggins argues that Synthes' product labels for Norian SRS and Norian XR were confusing, and that statements made to Synthes by the FDA in 2005 (months after these violations), did nothing to clarify those labels. He argues that a hypothetical reader of the SRS label "reasonably could conclude" that SRS could be used in the spine "on label in a variety of circumstances." Huggins Obj. p. 7. He argues further that the warning bullet that Synthes agreed to include on the XR label, "not intended for treatment of vertebral compression fractures" was not sufficiently clear to alert a person reading the label that XR was not intended for treatment of VCFs. Huggins concludes that Synthes' labels for SRS and XR were ambiguous and, based on

[2] It is, in any event, rather ironic that Huggins appears to be complaining that the government let him off too lightly.

the alleged ambiguity, asks the Court not to impose on him a sentence of imprisonment. Huggins Obj. p. 9.

As an initial matter, defendant Huggins' attempt to mitigate his crime in reliance on an allegedly confusing label amounts to an extraordinary act of gall. Labels are written by manufacturers to apprise users of limitations and dangers inherent in their products. Executives such as Huggins are directly responsible for any confusion that results from the language that their own companies employ on their labels. To the extent that they found the label confusing, each of the defendants was obligated to assure that such confusion was promptly clarified. Huggins' failure to do so is an additional reason to hold him responsible for the harm that Synthes' and Norian's products caused, not a basis on which to excuse him.

Moreover, and strikingly, Huggins does not state that *he* was confused by the SRS or XR labels. Neither does he point to any document or testimony that would show that anyone else at Synthes, including his three codefendants, was confused by the SRS or XR labels.[3] This is likely because the evidence shows that the Synthes and Norian employees found neither label to be the least bit confusing insofar as the crimes in this case are concerned. As cleared in December 2001, the SRS label warned that SRS was not to be mixed with any other substance.

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[3] Huggins' codefendant Bohner, in his objection to paragraphs 31 and 32, does cite selectively from testimony by two surgeons before the grand jury, to support his assertion that the SRS label was confusing. Bohner Obj. p. 4. However, nothing in the testimony that Bohner relies upon would support an inference that because those two surgeons claimed later, at the time of their testimony, that they found the SRS indication statement to be confusing, that anyone at Synthes was confused earlier, prior to the XR clearance, by the SRS indication statement, much less by the SRS warning that SRS was not to be mixed with any other substance. See pp. 48-49, below.

G. Mem. Exhibit 11, SRS label. That is why the first "test market,"[4] for SRS in the spine, was blatantly illegal: for, as the Synthes employees involved in that test market well knew, the warning on the SRS label absolutely forbade Synthes from teaching surgeons how to back-table mix SRS with barium sulfate.[5] And the individuals who approved the test market for SRS in the spine, including defendants Huggins, Higgins and Bohner, shared the lower-level employees' concerns that the test market for SRS in the spine was illegal.[6]

As cleared in December 2002, the XR label warned that XR was not intended for treatment of VCFs. Government's Amended Presentence Memorandum ("G. Mem.") Exhibit 46, XR label. This warning could not have been clearer.

Huggins suggests that the SRS indication statement – and later, the XR label even despite the warning – were broad enough to encompass use in the spine and were, therefore,

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[4] "Test market" is a term used by the defendants to describe a limited release of a product, to determine what customers prefer regarding *approved indications*. See G.Mem. 7, Synthes Product Development Test Market Policies. In this case, however, both the test market for SRS in the spine and the later XR test market were for the *unapproved* – and in the case of XR, warned-against – indication of treatment of VCFs.

[5] See, e.g., G. Mem. 33, memorandum from Nisra Thongpreda, who was the original group manager for SRS-R (identified in the indictment as Person No. 1), to defendants Huggins, Higgins and Bohner on SRS Training, dated June 4, 2002; G. Mem. 34, Powerpoint Presentation for SRS Training. The progress of the test market for SRS in the spine was discussed at a management meeting in September 2002, attended by defendants Huggins, Higgins and Bohner. See G. Mem. 35, MRB Meeting Spine Business Plan Review Agenda dated September 17, 2002, p. 2; G. Mem. 36, Powerpoint Presentation on Test Market for SRS in the Spine given at September 2002 MRB Meeting. The results of the test market for SRS in the spine were also discussed later at the July 18, 2003 Safety Meeting (led by defendant Huggins) and in the Safety Meeting materials, G. Mem. 38-42 and 37.

[6] Prior to approval of the test market for SRS in the spine, defendant Huggins was in contact with a medical consultant for Synthes who opposed the plan to conduct a test market for SRS in the spine, warning that it amounted to human experimentation. See G. Mem. Exhibit 32, emails from consultant to defendants Huggins and Higgins, and the CEO and owner of Synthes (identified in the indictment as Person No. 7). On May 30, 2002, after speaking with the consultant, defendant Huggins sent an email to defendants Higgins and Bohner, among others, citing his awareness of the plan and stating that he was now having second thoughts. See G. Mem. Exhibit 8.

confusing. But the evidence shows that the individual defendants were in no way confused. Not only did the XR label include a clear preclusion of the product for use in VCFs but, in dealing with Synthes, FDA was unequivocal and unwavering: SRS and XR were not approved for use in load bearing applications in the spine, specifically including surgeries for VCFs. In fact, this is exactly what Synthes told its physician customers in its February 2004 "Dear Surgeon" letters – signed by defendant Huggins – when it stopped the test markets. G.Mem. 76. The "Dear Surgeon" letter proves conclusively that Huggins well understood the identical indication statements on the SRS and XR labels, what they allowed and did not allow, and just how narrow those indication statements were.

Huggins' related claim he lacked criminal mens rea – given what he terms the FDA's "incoherent" interpretation of the meaning of Synthes' own label – is equally meritless. Initially, Huggins is relying on comments that FDA officials made at a meeting in 2005 (after Synthes had received an FDA Warning Letter about the conduct that is the subject of this criminal case) regarding what would be considered a cleared indication in the spine if various vertebroplasties were excluded. First of all, this meeting with the FDA was in 2005 – long after the fact. Moreover, even if his argument were based on FDA statements made during the relevant period, which it is not, his claim is disproved with a single document: the February 2003 e-mail exchange between Synthes and the FDA about the meaning of the label. See G. Mem. 53. In this email, the FDA is crystal clear that XR was not to be promoted for treatment of VCFs.[7] In any event, it is the manufacturer's duty in the first instance to propose label language

[7] In late February 2003, Vikki Hoffman, the Synthes regulatory employee who had handled the XR 510(k) submission (identified in the indictment as Person No. 11), sent an email to the (continued...)

for its product to the FDA, and to understand that language. See Riegel v. Medtronic, Inc., 552 U.S. 312, 319 (2008). It is not the FDA's duty to explain to the manufacturer the meaning of the manufacturer's own label – the manufacturer has a legal obligation to understand it.

At minimum, Huggins argues that the FDA's "reconstructed" interpretation of the cleared indications on the label as conveyed at that 2005 meeting shows that the label was ambiguous, counseling against more severe sanctions. He fails to mention, however, that the FDA had not previously interpreted the label any differently, nor was the agency ever asked whether certain procedures fell within the cleared indications. The FDA cannot refuse to clear a device that is substantially equivalent to a predicate device merely because the cleared indication is narrow and would have limited marketability. What is clear and unambiguous in this case is that the FDA knew that treating VCFs was a potentially huge market and therefore requested that Synthes agree to warn against such use on the XR label. This clear, unambiguous part of the label – the warning bullet – is the portion that the defendants disregarded.

C. Objections to Specific Paragraphs

1. Paragraph 6 of Bohner Presentence Report

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[7](...continued)
FDA, asking the FDA representative who had handled the clearance of XR whether, "as long as we clearly inform surgeons that Norian XR must be used with supplemental fixation (i.e., pedicle screws), we can indicate it [XR] for compression fractures in the spine?" Two days later, the FDA representative answered that Synthes could not, stating

> [u]se in treating compression fractures of the spine is not a cleared use for any of the bone void fillers (MQV product code). This indication is considered a new intended use and requires a PMA and clinical data. Even with proper fixation, the bone void filler in this situation (vertebral compression fractures) would not be used in a way that is 'non-intrinsic to the stability of the bony structure,' which is what the indication for the MQV bone void fillers require.

G. Mem. 53, email chain between Hoffman and FDA employee, which shows that, later, on October 16, 2003, this email was forwarded to defendant Walsh.

The government agrees that defendant Bohner pleaded guilty to Count 97 of the Indictment on August 13, 2009, not July 20, 2009.

2. Paragraph 7 of Presentence Reports

Defendant Higgins objects to the first sentence in this paragraph, which states that the instant offense occurred between in or around May 2002 and in or around July 2004. His objection is that he was no longer the President of Synthes Spine Division after January 2004. Higgins argues that after he left the presidency of Synthes Spine, he was no longer a responsible corporate officer of Synthes.

This objection should be rejected. As a factual matter (alleged in the Indictment [¶ 1d], and shown by documents), Higgins did not leave Synthes in January 2004. Rather, in February 2004 he took a new position, as Senior Vice President of Global Strategy for Synthes. In that position, Higgins still maintained responsibility for the unlawful and unauthorized clinical trials of the Norian cements that he had approved, overseen and participated in while President of Synthes Spine. Higgins' continuing responsibility for these past events is shown by his participation in a meeting on June 22, 2004, with defendants Huggins, Bohner and Walsh and other Synthes and Norian representatives, in order to plan a response to the FDA's 483 observations made after the FDA inspection. This meeting resulted in the false representations to the FDA by Norian and Synthes that: (i) the Norian XR "test market" was for cleared indications, instead of the treatment of VCFs; (ii) the Norian XR "test market" was not designed to obtain safety and efficacy information from surgeons about use of Norian XR to treat VCFs; and (iii) the two "test market" surgeon training meetings and the surgeon forum had not trained surgeons how to use Norian XR to treat VCFs. Indictment, ¶ 40, p. 37; Exhibit 1, attached.

3. Paragraph 19 of the Presentence Reports

This paragraph details the history of defendant Huggins' employment at Synthes. Huggins was the highest-ranking of the four Synthes executive defendants. This paragraph states that Huggins was hired by Synthes at the end of 1994. It states further that from 1999 through January 2004, Huggins was President of Synthes North America, and that from February 2004 until January 7, 2007, Huggins held the position of President of Global Synthes Spine Division. This paragraph then states how, until February 2004, each of the defendants reported, directly or indirectly, to Huggins: Higgins, the President of the Spine Division, reported directly to Huggins from 1999 through February 2004; Bohner, Synthes' Vice President of Operations, reported directly to Huggins from January 2002 until February 2004; and Walsh reported indirectly to Huggins, through Bohner, from August 2003 until February 2004.

Defendant Bohner objects, stating that defendant Walsh stopped reporting to him in January 2004, when Walsh began reporting to Fran Magee. The government agrees that, as noted in ¶ 22 of the presentence reports, Walsh reported to Bohner until January 2004, when Walsh began reporting to Fran Magee.

4. Paragraph 20 of the Presentence Reports

This paragraph details the history of defendant Higgins' employment at Synthes. It states that Higgins was hired by Synthes in September 1991, and that from 1999 through January 2004, Higgins held the position of President of Synthes' Spine Division. It continues that from February 2004 through May 2005, Higgins was Senior Vice President of Global Strategy for Synthes. It notes that Spine Division of Synthes ran the test market of Norian SRS in the spine, as well as the later Norian XR test market and unauthorized clinical trials.

Footnote four to ¶ 20 was written in response to an objection by Higgins. Footnote four states that in his initial objections, in April 2010, Higgins disagreed that "unauthorized clinical trials" occurred that would have violated the FDCA. Footnote four suggests that this objection contradicts a stipulation that Higgins made in his plea agreement (paragraph 9(i)). In that paragraph, each defendant agreed that the training of spine surgeons to use Norian XR in vertebroplasty-type surgeries to treat VCFs, as part of a so-called "test market" for Norian XR, was unauthorized clinical testing of Norian XR for the treatment of VCFs which violated the FDCA.

Defendant Higgins objected to footnote four, stating that it

> suggests a contradiction where none exists. It states that Mr. Higgins first agreed in his plea agreement, and then later disagreed in his objections to the draft PSR, that unauthorized clinical trials took place. In fact, Mr. Higgins merely pointed out that he did not believe *at the time* that the activities of the Spine Division constituted what the government later alleged to be "unauthorized clinical trials" and he never intended for the Spine Division to conduct activities that could violate the FDCA.

Higgins Obj. p. 2 (emphasis in original).

Apparently, Higgins does *not* dispute that the illegal, unauthorized clinical trials of Norian XR took place at all as a matter of fact (which would contradict his stipulation). He may be contending that (1) despite his position as President of Synthes Spine, he did not know about the nature of the Norian XR test market; or (2) he believed that the XR test market process was not the sort of gathering of data that rises to the level of a clinical trial; or (3) he believed that the XR test market gathering of data was perfectly legal.

Whichever of these alternatives that Higgins intends, he has raised a factual dispute that must be resolved by the Court at sentencing. The government respectfully suggests

that copious documentary evidence and witness testimony proves that Higgins well knew in August 2003 through January 2004 the nature of the XR test market. He knew that the activities that the Spine Division undertook during that period, while he was President, amounted to unlawful, not to mention unethical, clinical trials. Indeed, both Huggins and Higgins were told by their own consultant that their earlier SRS "test market" amounted to human experimentation. Although further notice of the illegality of his conduct was not needed, Higgins also knew a great deal more, including:

- that Norian XR bore a label warning that it was "not intended for treatment of [VCFs];"
- that in the so-called "test market" of Norian XR, Synthes trained spine surgeons to use XR in vertebroplasty-type surgeries to treat VCFs, notwithstanding the warning bullet; and
- that the Norian cements, as implants, were significant risk devices, which could not be tested on humans without prior approval of the FDA, which approval is given in the form of an Investigational Device Exemption ("IDE").

Even setting aside Higgins' knowledge of the grave patient risks presented by using XR to treat VCFs,[8] and even ignoring Higgins' sophisticated understanding of the two separate routes for obtaining the FDA's permission to market a medical device,[9] the evidence of

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[8] These included pilot studies showing that even small amounts of SRS could generate formation of large volumes of blood clot if SRS escaped from bone into the venous system ("the pilot studies"). See G. Mem. 31. See discussion of pilot studies at pp. 55-58 below.

[9] See e.g., G. Mem. 4, email from Higgins dated November 2, 2001; regarding a particular osteoporotic sheep study, he writes: "We need to evaluate this in light of any strategy to get clearance for (continued...)

Higgins' knowledge is overwhelming. In addition, the government mentions only in passing the compelling inferences that flow from Higgins' assistance in composing a false response to the FDA's 483 observations after the 2004 FDA inspection.[10] A person who believes that he has acted correctly, or does not know that his actions were wrong, does not find it necessary to lie about his actions. Focusing only on Higgins' knowledge of the Norian XR warning bullet, Norian's character as a significant risk device, what the spine surgeons were being taught at the "test markets," and the type of data that Synthes was gathering through the XR test market, it is clear that Higgins knew enough to know that he was participating in illegal conduct.

In fall 2002, Synthes submitted to the FDA a Special 510(k)[11] premarket notification for XR requesting clearance for a general bone void filler indication, listing Norian as the manufacturer, and telling the FDA that XR was substantially equivalent to SRS. Norian XR was cleared by the FDA on December 19, 2002, as a general bone void filler, with a label stating that XR was intended to fill only bony voids that were "not intrinsic to the stability of the bony structure" in the extremities, spine and pelvis, and specifically warning that XR was "not

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[9](...continued)
vertebroplasty. Although our initial strategy is to use the bone void filler indication, we should look at what it would take for a vertebroplasty indication. Do we need an animal study like this or something close? Can we get approval through a 510(k) with clinical data? Does it have to be a PMA? Once we have a strategy, we can decide on the merits of this particular study."

[10] As noted above, the false response stated that: the Norian XR "test market" was for cleared indications, not the treatment of VCFs; the Norian XR "test market" was not designed to obtain safety and efficacy information from surgeons about use of Norian XR to treat VCFs; and the two "test market" surgeon training meetings and the surgeon forum had not trained surgeons how to use Norian XR to treat VCFs. Indictment, ¶ 40, p. 37; Exhibit 1.

[11] A "Special 510(k)" is available to manufacturers who are seeking to market a modified version of their own previously cleared device. FDA Guidance is clear, however, that this expedited process cannot be used when the proposed change or modification to the device affects the intended use of the device.

intended for treatment of vertebral compression fractures." G. Mem. 46, Norian XR label as cleared December 19, 2002. The next day, Higgins sent the XR team an email congratulating them on getting XR approved, "designing such a smart plan, and executing it so well." G. Mem. 47, email from Higgins dated December 20, 2002.

Even assuming that he had managed to avoid becoming aware of the XR label's warning bullet before,[12] Higgins certainly learned of it no later than January 28, 2003, from an email sent to him by Bohner. That email, also copied to Huggins, appears to have been prompted by the first patient death, on January 13, 2003. See G. Mem. 52, January 28, 2003 email. In his email, Bohner urged that management notify the Spine sales force that XR should not be promoted for off-label uses, and argued that Higgins, as President of Spine, should send a proposed e-mail about off-label promotion to the Spine sales force. In his e-mail outlining the proposed communication to the Spine sales force, Bohner gave the defendants an example of which off-label uses were forbidden: "[f]or example, the FDA has required us to include the following warning in the product insert: 'not intended for treatment of vertebral compression fractures.'" From this email Higgins understood that Synthes could not promote use of XR to treat VCFs. Nonetheless, no communication that included both the warning bullet for XR, and an admonition that XR should not be promoted for off-label use, was ever sent to the Spine sales force.

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[12] On December 19, 2002, the Norian XR product manager emailed defendants Higgins and Bohner, along with others, to inform them that the FDA had cleared Norian XR through the Special 510(k) process. The approved label was attached. In addition, the Group Manager for Spine Regulatory, Barry Sands (identified in the indictment as Person No. 6), testified in the grand jury that he personally discussed the warning bullet with defendants Higgins and Bohner, before Synthes agreed to include that language on the label. Then Synthes resubmitted the Special 510(k) with the warning bullet – with the authority of upper management – on December 18, 2002.

On July 18, 2003, Synthes held a "Safety Meeting" called by defendant Huggins and attended by Huggins, Higgins, Bohner and others. According to the materials distributed at the Safety Meeting, as well as testimony of witnesses who attended, the declared purpose of the meeting was to decide whether Norian XR was safe enough to bring to market. Meeting participants heard a presentation by the XR product manager, Josi Hamilton, on a variety of patient safety issues: pilot studies conducted by researchers at the University of Washington, the two adverse hypotensive events that had occurred with Dr. Delamarter's patients, and the first death. Notes from the meeting show that the participants also discussed Synthes' failure to file an MDR on the first death, as well as the fact that there already had been three adverse events with a Norian product out of approximately thirty-four cases to date (a statistically significant figure). Faced with the choice whether to seek an IDE and a PMA, Huggins decided to continue the XR "test market" for use in vertebroplasty-type procedures to treat VCFs that had begun in late summer of 2002 with SRS, with the goal of having "test sites" publish results of surgeries. Materials distributed in advance of the July 18, 2003 Safety Meeting are G. Mem. 37; the Powerpoint shown at the Safety Meeting is G. Mem. 38; minutes of the Safety Meeting, which show that defendants Huggins, Higgins and Bohner received them, are G. Mem. 39, 40 and 41; and handwritten notes taken during the Safety Meeting by Synthes consultant Harold Aberman DVM (identified in the indictment as Person No. 10), are G.Mem. 42.[13]

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[13] Defendant Bohner also took notes of the discussion held at the Safety Meeting, in the form of a diary entry, which including the following: "Ken Lambert: thinks there's a massive cover up + many clinical problems, accuses us of not doing MDR reports." "JH [Josi Hamilton, the XR product manager]: cement leakage is main concern." "Helfet [Synthes Board of Director member, Dr. David Helfet]: after 200 to 300 patients in TM, make launch decision." "Abstract [of University of Washington research]: 'lethality . . . Norian . . . embolization' is potentially damaging." See G. Mem. 80, (continued...)

The Safety Meeting materials discuss the earlier test market for SRS, in which Synthes Spine employees had trained spine surgeons to mix SRS with barium sulfate and use the resulting mixture to treat VCFs, calling that test market "Phase I." The materials explain further that surgeons were chosen to participate in the upcoming test market for Norian XR, "Phase II," based on "publication interest, affiliation with treating vertebral compression fractures, and working with thought-leaders in this market segment." G. Mem. 37. The Competitive Activity section of the Safety Meeting materials contains a detailed discussion of the treatment of VCFs, noting that the aging of the baby boomer population and an increasing incidence of osteoporosis has created an "enormous flux of companies strategizing to provide products for treating. . . [VCFs]." G. Mem. 37. Treatment of VCFs is the only intended use for Norian XR mentioned in the Competitive Activity section; and overall, the focus of the Safety Meeting materials is on the treatment of VCFs. G. Mem. 37.

The minutes of the Safety Meeting show that the pilot studies were discussed, and that follow-up studies proposed by Dr. Chapman (Doctor No. 3) had not yet been begun. The participants were concerned over the abstract that Drs. Chapman and Mirza (Doctor Nos. 3 and 2, respectively) had written of the article they wanted to be published by ORS (Orthopaedic Research Society); the minutes state, "[p]otential to start on the defensive based on the language in the abstract." This refers to the finding that Norian cements appeared to cause blood clots.[14] G. Mem. 39, 40, 41. See G. Mem. 37, Safety Meeting Materials, ORS abstract, p. .000369.

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[13](...continued)
Bohner Diary entry for July 18, 2003.

[14] The pilot studies are discussed in detail at pp. 55-58 below, in connection with the objection to paragraph 34E.

The power point shown at the Safety Meeting is titled "Norian XR, Addressing the Clinical Concerns." G. Mem. 38. The second slide, stating the purpose of the meeting, asks "[i]s it safe to proceed to market with this product?" G. Mem. 38, p. 2. The minutes of the Safety Meeting show that the participants discussed whether to begin an approved clinical study for FDA "approval in vertebroplasty/kyphoplasty." Notes of another participant, Harold Aberman, show that detailed plans were made to gather clinical data from surgeries in the test market, to determine whether XR was more safe, or less safe, than PMMA in treating VCFs.[15] So in the face of mounting evidence that the Norian cements might cause blood clots, and a high rate of adverse events, the meeting participants, led by Huggins, chose the illegal route, deciding not to seek the FDA's approval for the vertebroplasty indication, but instead to "enlarge Norian XR test market":

> **Recommendation**:
>
> Proceed with current test market plan. Need to establish a larger case base (need 200-300+ cases prior to release) at multiple sites. Test market feedback and clinical experience will determine if we proceed with November launch plan. Gather as much info as possible from test sites to ensure ability to publish findings.
>
> **Test market will provide a degree of confidence in what we expect our complication rate to be – especially versus PMMA. This will help us determine our associated level of risk and decide what level is too high.**

G. Mem. 39, p. 2 (emphasis supplied).

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[15] After noting, "Look into Nisra Letter from Ken Lambert," Aberman's notes go on to discuss the collection of clinical data from test market surgeries: "If adverse events do happen, they are very acute. Dr. Helfet supports controlled roll-out with data collection of acute data which will be collected; this will likely be published by test market sites. Launch is planned in November. What is expected by November? Several hundred by then. Base decision on the acute reaction to first 200-300 patients and determine if similar to PMMA. . . . Be diligent with collecting data on adverse events. Meanwhile, discourage off-label use where cannot get the data. What is responsibility if used off label? Not to participate as a company if used off label." G. Mem. 42.

On August 14, 2003, the day before the first surgeon training meeting of the test market, defendants Huggins, Higgins and Bohner, other Synthes employees and a number of surgeons held a strategic planning meeting on XR, at which the issue of an FDA-approved clinical study of XR was raised again. The meeting minutes and participant testimony show that Higgins reviewed the current indications, "and on-going studies that will prove safety of the technique with Norian XR" i.e., the test market. Huggins noted that Synthes had a "poor record of PMA approvals." Defendants Huggins and Higgins directed that the XR "test market" would continue, despite a presentation made at the meeting on vertebroplasty and XR and a recommendation by one of the doctors that an FDA study of XR be conducted to gain approval for vertebroplasty.[16] See G. Mem. 55.

On August 15 and 16, 2003, Synthes held the first surgeon training meeting of the "test market," in San Diego, California. Spine surgeons were selected to attend based on their experience in treating VCFs, and their expenses to travel to and attend the training were paid by Synthes. Lectures and power point presentations were given to the attendees concerning the use of XR in surgeries to treat VCFs, and a cadaver lab was held during which the surgeons injected XR into the vertebral bodies of cadavers. At this surgeon training, Synthes Spine personnel distributed notebooks to the attending spine surgeons which thanked them for participating in the XR "test market," and gave the sales consultants forms[17] for reordering XR ("test market reorder

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[16] Defendant Bohner noted this recommendation in his diary as "IDE for vertebroplasty." See G. Mem. 80, Bohner Diary entry for August 14, 2003.

[17] The information that was requested in the "test market" reorder forms included clinical data on the warned-against indication; whether the patient had a previous VCF; whether the bone was (continued...)

forms" or "TM forms"). The sales consultants were also instructed, repeatedly, that they could not reorder XR unless they filled out the "test market" reorder forms with information about each surgery performed with XR. At the first surgeon training, Synthes did not inform the trainee surgeons of the first death, the other adverse events, or the pilot study results. See G. Mem. 56 (notebook distributed at first surgeon training meeting); G. Mem. 57 (blank "test market" reorder form).

On August 28, 2003, the Norian XR product manager e-mailed defendants Higgins, Bohner and others: "Norian XR is officially released to Test Market. We shipped to 13 Spine sites Wednesday afternoon (8/27), and have 4 cases scheduled for Friday (8/29)." G. Mem. 58. On September 10, 2003, the XR product manager e-mailed Higgins that one XR test market surgeon had had two cavity creation surgeries with XR that day and that another surgeon was to have such a surgery the following day. She further forwarded to Higgins a report of six other such surgeries and related shipment of product. See G. Mem. 59. These documents and others show that Higgins received frequent updates from the XR product manager on the status of the test market VCF surgeries.

On September 19, 2003, when a spine surgeon, Dr. Paul Nottingham (identified in the indictment as Doctor No. 5), used XR in a surgery using cavity creation instruments to treat VCFs, the patient died on the operating table after suffering a hypotensive episode ("the second death"). A Synthes sales consultant was present during the surgery. Dr. Nottingham noted a cement leak, and believed that it was the cause of the episode, and could not rule out XR as a

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[17](...continued)
osteoporotic; the number of levels treated (referring to levels of the vertebrae); the age of the fracture; the percentage of compression; and whether postural reduction was attempted. G. Mem. 57.

cause of the second death. See G. Mem. 62, Minutes of September 23, 2003 Meeting. Synthes and Norian filed an MDR on the second death that was vague as to the surgery and its details.[18] Again, neither company had an independent medical expert analyze the death.

Despite the second death, the second surgeon training meeting of the "test market" on September 19 and 20, 2003 continued. Higgins attended this meeting, held in Charlotte, North Carolina. See G. Mem. 63, 64. The second training followed a format identical in substance to the first surgeon training; again the spine surgeons invited were selected by Spine Division personnel and the sales force based on their experience in treating VCFs; and the surgeons' expenses to travel to and attend the training were paid for by Synthes. At the second surgeon training, no one informed the trainee surgeons of either of the first two deaths, the other adverse events, or the pilot study results (although the XR product manager called some surgeons later to inform them of the second death).

On September 23, 2003, defendants Huggins, Higgins, Bohner and Walsh, among others, attended a meeting focused on what would be done with the XR test market in the wake of the death of Dr. Nottingham's patient. Huggins was the most senior manager present at this meeting. See G. Mem. 65, 66, agenda for September 23, 2003 meeting. The evidence also shows that defendants Huggins, Higgins and Walsh attended another meeting on Halloween, October 31, 2003, at which the death of Dr. Nottingham's patient and additional findings from the University of Washington were both discussed. See G. Mem. 67, Colleen Flescher of

[18] This MDR and the MDR on the third death were brief, vague and did not mention the terms "vertebroplasty," "kyphoplasty," or "vertebral compression fracture" in order to conceal from the FDA and spine surgeons the fact that the second and third deaths had occurred during surgeries to treat VCFs, in which cement leakage had been noted.

Synthes Spine's handwritten notes of meeting October 31, 2003. The outcome of those meetings was that despite the new death and further results from the University of Washington of the same tenor as before, indicating that the Norian products might pose serious risks if used in the spines of humans, the studies on humans with Norian XR in the test market would continue.

On September 26, 2003 – as reported to all four defendants a few days later – another spine surgeon, Dr. Lane, told the XR product manager Josi Hamilton and the consultant, Dr. Aberman, that he believed that XR was "potentially dewatering and causing episodes of hypotension." He also stated that, because the Norian XR "test market" was collecting information from surgeons performing surgeries to treat VCFs, he believed that Synthes was required to go to each institutional review board ("IRB") of each hospital participating in the "test market." Dr. Lane also told these Synthes representatives that, in light of the company's "test market" activities, the company should go to the FDA immediately to negotiate the removal of the warning on the XR label, "not intended for treatment of vertebral compression fractures." Dr. Lane also stated that, in his view, Synthes had risk management problems and needed more oversight of its clinical and compliance issues. Defendants Huggins, Higgins, Bohner and Walsh were all informed of Dr. Lane's views within days. See G. Mem. 68, email chain dated October 1, 2003.

The evidence summarized above (pp. 14 through 22) shows that defendant Higgins knew that the so-called XR "test market" amounted to unauthorized clinical testing of XR, in violation of law. That is, he knew the nature of the XR test market; understood that the XR test market process was in fact the sort of gathering of data that rises to the level of a clinical

trial; and recognized that the XR test market and associated gathering of data violated the law.[19]

5. Paragraph 21 of the Presentence Reports

This paragraph details the history of defendant Bohner's employment at Synthes. It states that Bohner was hired by Synthes in June 1997, and that from January 2002 through 2005 he served as Vice President of Operations for Synthes, in which position he reported directly to defendant Huggins until February 2004. Paragraph 21 states that as Vice President of Operations, Bohner was responsible for overseeing operations throughout the entire organization and its several divisions, including the Spine Division, which ran the Norian SRS for the spine and XR test markets and unauthorized clinical trials. This paragraph notes that the operational functions that Bohner oversaw included manufacturing, logistics, regulatory affairs, human resources, shared services and graphics productions.

Defendant Higgins objects to the statement that the Spine Division ran unauthorized clinical trials, and refers to his earlier objection to paragraph 20. The government's

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[19] If Synthes had decided to conduct its clinical research legally, it would have had to obtain FDA approval *prior* to the commencement of the research. The FDA would have reviewed the Investigational Plan, which would have included the following: (1) a protocol, demonstrating the scientific soundness of the proposed methodology; (2) a risk analysis based on the age, sex and condition of the proposed patient population and a plan to minimize such risks; (3) a description of the monitoring procedures that would be in place to protect the subjects; (4) all forms and informational materials to be used to gain informed consent of the subjects; and (5) information on the Institutional Review Board ("IRB") employed to provide independent oversight of the investigation.

The fact that NONE of these important patient safeguards were employed is shocking, and was unethical as well as illegal. Perhaps the most shocking omission, however, is the complete lack of regard for the patients who at the very least should be given the choice about whether they want to participate in a clinical investigation. This choice should be an informed choice, where the foreseeable risks are described and the alternative treatments are disclosed. In addition, the subjects should be given an explanation of who to contact for answers to pertinent questions about their rights as research subjects, including who to contact if there is a research-related injury.

response is the same as that concerning ¶ 20, above (see pp. 12-13, and response pp. 14-22). Putting aside the earlier test market for SRS in the spine, to which the government believes this objection is not addressed, overwhelming evidence shows that as President of the Spine Division, Higgins knowingly approved, participated in and supervised the later XR test market, which all defendants have stipulated in the plea agreements constituted unauthorized clinical trials. That same evidence shows that defendant Higgins was well aware that the test market was thoroughly illegal, as the XR test market involved a concerted effort by Synthes Spine to teach surgeons to use XR to treat VCFs, contravening the XR label. The fact that decision-makers at Synthes, including defendants Higgins, Bohner and Huggins, held so many meetings about whether or not the test markets (both SRS and XR) should go forward, is itself powerful evidence that defendants Higgins, Bohner, and Huggins knew that what they were planning was illegal (just as the Spine professional group employees had told the XR project manager back in December 2002, before the clearance of Norian XR. G. Mem. 19). The possibility that Higgins might not have had foreseen precisely how the prosecuting authorities would characterize his crime later does not matter. He knew that the Spine Division and the company had planned, and were executing, a scheme in which surgeons would experiment on humans – most of whom were elderly and frail – without the FDA's knowledge or consent, so that Synthes could gather data in order to assess the risk level of using Norian XR to treat VCFs, and to determine whether, in the company's view, that risk level was too high.

Defendant Bohner also objects to this paragraph, "to the extent that [it] suggests that [he] led or managed the Spine Division. . .Mr. Bohner never held a position in the Spine Division, nor did he lead or manage the Spine Division. As Vice President of Operations, Mr.

Bohner was not involved in the Spine Division more than any other product division of the company."

This objection lacks merit. Paragraph 21 does not suggest that defendant Bohner "led or managed" the Spine Division. It states that he had oversight authority over operations of "several product divisions, including the Spine Division. . ." The government cannot speak to defendant Bohner's involvement in the other divisions of Synthes,[20] but notes that Bohner kept a work diary in which he made numerous, often detailed, entries about SRS and XR, and later, the FDA inspection in May - June 2004. G. Mem. 80.

6. Paragraphs 23-26 of the Presentence Reports

These paragraphs, titled "The Medical Context," describe vertebral compression fractures ("VCFs"), the surgery called vertebroplasty developed to treat VCFs, in which a surgeon injects a mixture of bone cement and a contrast agent into the vertebral body to support

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[20] The government notes that prior to 2000, Synthes had three main divisions: Spine, Maxillofacial, and Trauma. Each of these three divisions had its own sales force, reporting to regional managers, its own separate launch team, and its own separate regulatory personnel, who reported to a vice president of regulatory affairs, James McCracken, and through McCracken to defendant Bohner. Bohner, in turn, reported to defendant Huggins, the President of Synthes North America, until February 2004. Defendant Higgins reported to Huggins as well, until the end of January 2004. Defendant Walsh, who was hired as a regulatory consultant in the Spine Division in June 2003 and became the full-time Director of Regulatory and Clinical Affairs in the Spine Division in August 2003, reported directly to defendant Bohner until January 2004, then to Fran Magee, and then to defendant Huggins directly starting in early June 2004.

Throughout the time period covered by the indictment, 1999 through late 2004, Synthes operated without a marketing department; the responsibility for preparing marketing and promotional materials for the devices fell primarily to the product development personnel in each division, as aided by that division's launch team.

In mid-1999, Synthes acquired the Norian Corporation, manufacturer of Norian SRS and CRS. In 2000, a fourth division, Osteobiologics, was formed; Osteobiologics, unlike the three other divisions, had neither its own sales force nor its own regulatory personnel.

the fractured bone, and the variant of vertebroplasty, called kyphoplasty, in which a balloon is inserted and inflated in a collapsed vertebral body, restoring the bone's height before the cement injection. These paragraphs also note that the term "vertebroplasty," when used in a broad sense, describes any percutaneous (minimally invasive) surgery in which a mixture of bone cement and a contrast agent are injected into a vertebral body to stabilize fractured bone and relieve pain.

Defendant Huggins objects to these paragraphs because they do not "reflect the fact that surgeons make independent medical judgments." Huggins Obj. p. 8. Rather than characterize the medical judgments made by surgeons, the government suggests that it is more accurate to say, as reflected elsewhere in the PSRs (e.g., paragraphs 9g; 31), that because the FDA does not regulate the practice of medicine, surgeons may, in their practice of medicine, use medical devices outside of their cleared or approved indications. Furthermore, it is this very fact – that the FDA does not regulate how doctors use approved and cleared products – that the defendants exploited in their effort to obtain for XR an FDA clearance with the word "spine" in the label, so that they might have plausible deniability for discussing XR with spine surgeons who treated VCFs, when their true intended use for XR all along was in surgeries to treat VCFs. This effort was thwarted because the FDA continued to request that Synthes include labeling that specified that load bearing indications such as vertebroplasty were not included in XR's indications, until Synthes – through Spine Division personnel who reported to Higgins – submitted the warning bullet against VCF use.

7. Paragraph 27 of the Presentence Reports

This paragraph recounts how, starting in spring 2000, Synthes and Norian conducted market research on the use of Norian products to treat VCFs, and interviewed spine

surgeons, neuroradiologists and neurosurgeons who had used an acrylic bone cement, polymethylmethacrylate ("PMMA") off-label in vertebroplasty and kyphoplasty surgeries to treat VCFs. Synthes asked these doctors whether they had used SRS in such surgeries, how SRS had performed in this indication, and – for the many surgeons who had used only PMMA – how often they might use SRS in such surgeries, among other questions. The paragraph continues that the purpose of these interviews was to create a market for the use of a version of SRS with radiopaque barium sulfate in vertebroplasty and kyphoplasty surgeries to treat VCFs.

Defendant Bohner objects to paragraph 27, stating that he "did not approve, direct or participate in the surgeon interviews. The market research was carried out by the Spine Division. As noted, Mr. Bohner never held a position in or managed the Spine Division." Bohner Obj. p. 2.

Defendant Higgins objects to the last sentence in paragraph 27, which states that the purpose of Synthes' market research was to "create a market" for the use of SRS to treat VCFs. Instead, according to Higgins, "the evidence shows that Synthes performed permissible market research to understand physicians' needs." Higgins Obj. p. 2.

Higgins' objection is without merit and should be rejected. The short answer to his objection is that, as Higgins was told by Synthes Regulatory in September 2001 – and as he agreed – this so-called "market research" constituted off-label promotion of SRS. Defendant Higgins directed that the surgeon interviews take place, see his SRS For Spinal Applications, Action Plan Memorandum, co-authored by Higgins in February 2000. G. Mem. 3. Because SRS had no spine indication, Higgins knew that these interviews were off-label promotion of SRS when he directed his subordinates in the Spine Division to conduct them. And when, shortly

after the surgeon interviews were completed, Synthes Regulatory told defendant Higgins that such interviews could not be done because they were off-label promotion of SRS, Higgins agreed. G. Mem. 18.[21] (but he did not tell the Vice President of Regulatory that the interviews had already happened). Higgins' agreement that such interviews were illegal shows that he knew as early as the fall of 2000 that this was not permissible market research.

Defendant Bohner attempts to distance himself from the surgeon interviews by

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[21] Here is the longer answer. Synthes had traditionally manufactured metal medical devices that are properly characterized as "hardware," and had an established market presence in trauma products, but lacked a market presence in osteobiological products. Indictment ¶ 35. Norian Corporation, by contrast, manufactured bone cements, and had developed SRS (Skeletal Repair System) and CRS (Cranial Repair System), identically formulated calcium phosphate bone cements. SRS was a Class III device that had been approved by the FDA under a PMA to be marketed for use in the distal radius (a long bone in the arm), while CRS was a Class II device that had been cleared by the FDA to be marketed for filling defects in the skull. Once Synthes purchased Norian in June 1999, Synthes began exploring new intended uses for the Norian cements, with an eye toward eventually obtaining an indication for use of Norian in the spine. Indictment ¶ 1b.

From the beginning, Synthes' intended market for Norian was in surgeries to treat VCFs. Synthes estimated that there were one-half million Americans suffering from that condition in 2000. Due to the aging of the baby-boom population, the market for treatment of this very painful condition was seen as a growing and lucrative one that was largely untapped at the time. Although PMMA, mixed with barium for greater radiopacity, was used in surgeries to treat VCFs, it had drawbacks, leading medical device manufacturers to begin exploring alternative bone cements, including those made from calcium phosphate, which did not share PMMA's perceived disadvantages. Prior to April 2004, during the relevant period here, no bone cement (acrylic or calcium phosphate) was cleared or approved by the FDA for use in treatment of VCFs in vertebroplasty and kyphoplasty surgeries. On April 1, 2004, for the first time, the FDA cleared an acrylic bone cement for use in kyphoplasty surgeries. Indictment ¶ 34.

The market research that defendant Higgins defends as "permissible" involved Spine Division employees interviewing surgeons who used PMMA off-label in vertebroplasty and kyphoplasty surgeries to treat VCFs, about whether they had used SRS in such surgeries, how SRS had performed in this indication, and – for the many surgeons who had used only PMMA – how often they might use SRS in such surgeries, among other questions. The market research was summarized in the Vertebroplasty Market Investigation Executive Summary ("Vertebroplasty Summary"), G. Mem. 1. As explained above, Synthes could not legally promote SRS for use in surgeries to treat VCFs. And since PMMA was the product that nearly all of the surgeons used in their surgeries to treat VCFs, see G. Mem. 1, pp. 1, 7, it is difficult to see what business reason would prompt Synthes Spine to ask surgeons who used PMMA about using SRS instead, except the desire to create a market for the use of a more radiopaque version of SRS in treating VCFs. All of this illustrates that from the beginning, Synthes' true intended market for XR was an unapproved, and eventually warned-against, use, i.e., in surgeries to treat VCFs.

stating that he neither approved, directed nor participated in them. But Bohner does not say that he was unaware of them; and in fact he certainly learned of them shortly after they happened, in fall 2000, when a Synthes Regulatory employee, Michael Sharp, Ph.D., brought them to his attention.

In fall 2000, Sharp, a vice president in regulatory reporting to James McCracken, who in turn reported to Bohner (Sharp is referred to in the indictment as Person No. 3), had spoken to defendant Higgins and Kevin Carouge, president of Osteobiologics, about such surgeon interviews. Sharp told Higgins and Carouge that Synthes personnel should not interview surgeons and ask if they had used SRS in vertebroplasty or kyphoplasty surgeries, how it had performed in such surgeries, possible ways to improve the performance of SRS in such surgeries, how they might use SRS in such surgeries, because it would constitute illegal off-label promotion of SRS, and Higgins and Carouge agreed with Sharp. G. Mem. 18. Sharp reported this situation to Bohner. G. Mem. 18. And earlier, in August 2000, when Sharp had first learned – to his alarm – about a proposed "test market" for SRS in vertebroplasty, which was unknown to Regulatory at the time, Sharp advised Higgins, Bohner and Carouge that

> we cannot promote the use of SRS for unapproved indications, and this is especially true for use in the spine, where FDA has previously made it clear to Norian that any intraspinal use would require additional approval.

G. Mem. 17.

This directive from regulatory – do not promote SRS for use in the spine – was clear and obviously correct. But defendant Bohner's response is telling. He forwarded Sharp's email to defendant Huggins, commenting: "FYI, we need to be careful if a 'test market' is being planned for SRS & the spine. We have no indication for this, as you know!" Bohner does not

say that Synthes must not conduct a test market for SRS and the spine, or ask Huggins to stop it from happening. Instead, Bohner advises Huggins that "we" need to be careful, assuming that the test market will go forward with Huggins' blessing, despite its illegality. G. Mem. 17.

8. Paragraph 28 of the Presentence Reports

This paragraph discusses a management meeting attended by defendants Huggins and Higgins, along with other top Synthes officials, in November 2001, at which the Spine Division made a presentation on how Synthes could obtain the FDA's approval for use of Norian to treat VCFs. The Spine Division reported that the IDE and PMA process would take 36 months and cost Synthes at least $1 million. The paragraph continues that after this meeting, the CEO and major shareholder of Synthes directed that Synthes would not pursue FDA approval of Norian to treat VCFs via an IDE and a PMA, but instead would press on with a "test market" for use of an extra-radiopaque version of Norian in the spine, with the aim of trying to persuade surgeons to publish on the results of their surgeries. The paragraph concludes that Higgins followed this directive, approving an SRS test market in the spine ("Phase I"), that is, a test market for SRS mixed with barium sulfate to treat VCFs, which began in late summer 2002. By May 2002, Huggins was aware of, and involved in, the process of approving the SRS test market in the spine.[22]

Defendant Bohner objects, stating that he did not attend the November 2001 management meeting discussed in this paragraph. The government agrees that so far as its

[22] This last sentence of paragraph 28 should add that by the end of May 2002, Higgins and Bohner, as well as Huggins, were aware of, and involved in the process of approving the SRS test market in the spine, as is shown by the evidence summarized below.

investigation showed, Bohner did not attend the November 2001 meeting. Because ¶ 28 does not say that he did, this aspect of Bohner's objection is meritless. The government notes, however, that the Spine Division's IDE presentation was based upon a draft vertebroplasty clinical study outline that had been reviewed and approved by Bohner in October 2001.[23] See G. Mem. Exhibit 6, e-mail chain between Sands and defendant Bohner dated October 17, 2001 and October 22, 2001, and attached outline of clinical study. From this outline Bohner knew, if he had not known before, that SRS-R (the product in development that was eventually cleared as XR) would not be cleared by the FDA for treatment of VCFs via a 510(k) pre-market notification, but could only be approved by the FDA for that indication via PMA, if supported by clinical trials.

So regardless of Bohner's absence from the November 2001 management meeting, he knew the details of the IDE proposal presented by the Spine Division, because he had discussed it with Sands and approved it. Thus Bohner knew of the problem faced by Synthes: the intended market for Norian was for an unapproved use, i.e., in surgeries to treat VCFs. Defendants Huggins, Higgins and Bohner recognized early on – and certainly no later than the November 2001 meeting – that there were two possible solutions to this problem: (1) the legal solution, which was to secure FDA approval of XR for use in vertebroplasty-type procedures to treat VCFs, via the long, costly PMA approval process, after an IDE to investigate the safety and efficacy of the product; and (2) the illegal solution, which was to obtain clearance through the shorter 510(k) process by concealing the true intended use, then to promote XR for

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[23] When Bohner asked the author of the outline, Barry Sands, Group Manager of Spine Regulatory, what the company would use for a "control" in the clinical trial, Sands (who reported to Bohner), responded that the control would have to be standard medical practice – to treat non-surgically – because "[c]urrently no device controls exist. PMMA is used off-label. Thus, if we used PMMA it would be considered another experimental cohort." G. Mem. 6.

use in VCFs through limited, low-cost "test markets" during which the company would attempt to fly below the FDA's radar while evaluating the safety and efficacy of the products in unsupervised clinical trials and judging their success according to its own standards. The November 2001 meeting was the first of many at which the defendants and others at Synthes struggled with this clear choice. Unfortunately, each time they chose the illegal solution.[24]

Concerning the test market for SRS in the spine, defendant Bohner objects further to paragraph 28, that he

> disagrees that his lack of awareness at the time that the test market would be a violation of the law contradicts stipulations that he made in his plea agreement that the test markets were in fact illegal. Mr. Bohner did not attend a test market training session; did not supervise the employees who organized and conducted the test market sessions; and we are not aware of any evidence that Mr. Bohner reviewed or approved the test market presentations or the evaluation forms used for them. However, Mr. Bohner pleaded guilty to a strict liability, responsible corporate officer misdemeanor, agrees that the test markets were illegal, and accepts responsibility for the offenses including the part relating to the test markets.

Bohner Obj. p. 3.

Defendant Higgins objects "to the suggestion in this paragraph that a test market is improper. There is nothing inherently wrong with conducting a limited release of an approved product, which physicians, utilizing medical judgment, can choose to use on or off label as they see fit. Mr. Higgins never intended for the Spine Division to conduct activities that could violate

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[24] Defendants Huggins, Higgins and Bohner made a conscious and deliberate decision to choose the illegal solution and got caught. That is, Synthes deliberately bypassed the requirement that it obtain permission from the FDA to conduct clinical trials of its XR device on human beings for an unapproved use – permission that the evidence repeatedly shows that these three defendants, and later, defendant Walsh, knew was needed. With the so-called "test market," the defendants tried to save the company time and money by cutting out the FDA's oversight of clinical trials of the XR device. They did this for two reasons: to rush XR to the market first, before its competitors, and to generate published studies that Synthes could use later to convince other surgeons to use XR off-label to treat VCFs.

the FDCA." Higgins Obj. p. 3.

Higgins' objection misses the point. First of all, as the defendants have stipulated, manufacturers of significant risk devices may not legally conduct clinical trials or investigations on their products in the United States without first obtaining the FDA's permission to do so by means of an IDE (plea agreement ¶ 9c; Indictment ¶¶ 8-10). Second, as the defendants have also stipulated, this particular test market, the SRS test market for the spine, was illegal because Synthes employees trained spine surgeons to mix SRS with barium sulfate and to use the resulting product in vertebroplasty-type surgeries to treat VCFs, notwithstanding that the label of SRS stated that the product was not to be mixed with any other substance (plea agreement ¶ 9h; Indictment ¶ 82, Overt Acts 1, 2).[25] As for defendant Higgins' profession that he "never intended for the Spine Division to conduct activities that could violate the FDCA," this again raises a factual issue that the Court must resolve at sentencing.

Defendant Bohner's objection concerning the test market for SRS in the spine is similar to Higgins', and mirrors the earlier objection made by Higgins about the later XR test market, which is addressed at pages 14 through 22 above. Apparently, Higgins and Bohner do *not* dispute that the illegal test market for SRS in the spine ("Phase I") took place at all as a

[25] FDA regulations do provide an exemption to obtaining an IDE for "consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk." 21 C.F.R. § 812.3(c)(4). A test market, however, cannot be for an investigational use of the device. 21 C.F.R § 812.7(a). This includes a modification that would require a new 510(k), or a new intended use. 21 C.F.R. § 807.81(a)(3). In this case, Higgins' claim that the SRS test market was somehow an appropriate test market is refuted by the fact that the product was being tested for safety and efficacy, put subjects at risk and, most importantly, was to test the product in a new intended use. What is perhaps most egregious about this scheme was that the defendants tried to exploit the exemption allowed test markets to not only escape FDA oversight, but also to avoid (i) scrutiny by institutional review boards, (ii) regulations promulgated to protect human subjects, and (iii) having to obtain the informed consent of the subjects themselves.

matter of fact (which would contradict their stipulations in paragraph 9h of the plea agreements). Higgins and Bohner may be contending that (1) despite their positions as President of Synthes Spine Division and Vice President of Operations of Synthes, respectively, they did not know about the nature of the test market for SRS in the spine; or (2) they believed that the test market for SRS in the spine was perfectly legal.

Whichever of these alternatives that these defendants intend, they have raised a factual dispute that must be resolved by the Court at sentencing. The government respectfully suggests that copious documentary evidence and witness testimony proves that both Higgins and Bohner (as well as Huggins) understood in May 2002 through December 2002 the nature of the test market for SRS in the spine. They knew that the activities that the Spine Division undertook during that period amounted to unlawful adulteration of SRS. Since the SRS label bore the warning that SRS was not to be mixed with any other substance, and the test market required that Synthes instruct the spine surgeons how to back-table mix SRS with barium sulfate, the radiopaque agent, before teaching them how to use the resultant mixture in surgeries to treat VCFs, on its face the SRS test market was unlawful. This blatant illegality troubled not only the Spine Product Development employees who were tasked with carrying out the test market, but also their superiors in the Synthes management who decided to approve it: Huggins, Higgins and Bohner.

As stated in ¶ 29 of the PSR, in December 2001, Synthes had obtained from the FDA 510(k) clearance for SRS as a general bone void filler, with a label stating that SRS was intended to fill only bony voids that were "not intrinsic to the stability of the bony structure" in the extremities, spine and pelvis, and further warning that SRS was not to be mixed with any

other substance. G. Mem. 11, SRS label. In connection with the SRS 510(k) submission, Synthes never told the FDA that the company intended to market SRS for load-bearing spine use such as in surgeries to treat VCFs. And at the time of the SRS clearance, defendants Huggins, Higgins and Bohner knew (from the IDE proposal presented by the Spine Division at the management meeting in November 2001, G. Mem. 5, 6) that this clearance did not permit Synthes to promote SRS for treatment of VCFs – that could only be done by means of an IDE and a PMA, the long form of approval.

Furthermore, Higgins, Huggins and Bohner were all familiar with the SRS label, in particular its warning that SRS was not to be mixed with any other substance.[26]

In addition, independent of violating the no-mixing warning on the SRS label, patient risk issues made the SRS test market both illegal and unethical, and the defendants knew this. Prior to approval of the test market for SRS in the spine, defendant Huggins was in contact with Dr. Kenneth Lambert, a medical consultant for defendant Synthes who opposed the plan to conduct a test market for SRS in the spine, warning that it amounted to human experimentation. In emails that Dr. Lambert sent in early June 2002 to a Synthes Product Development employee, then forwarded to Huggins, Higgins and the CEO, he stated:

> [y]ou have presumably been given the green light to begin a controlled study on using SRS with vertebroplasty using the new cavitation instruments. I am not questioning the wisdom of that decision, but question what has really changed in our understanding of the material since the moratorium [that Dr. Lambert believed Synthes to have put in place due to safety concerns about use of SRS in the spine] began? Nothing, except an article in JBJS of a death using CRS (SRS). In my respectful opinion, giving SRS directly to a

[26] In addition, interviews and grand jury testimony show that defendant Higgins had conversations with Spine division employees concerning the off-label nature of the SRS test market, and personally (though through an intermediary employee) allayed staff concerns about the off-label nature of the project.

> surgeon for him to use without any protocol (control), is not a controlled study: and given the other issues I have mentioned, this action amounts to human experimentation whose only defense seems to be that it will be a small study.

G. Mem. 32, emails from Dr. Lambert to defendants Huggins and Higgins, and the CEO.

The evidence shows that defendant Huggins took Dr. Lambert's concerns seriously for, on May 30, 2002, after speaking with Dr. Lambert, Huggins sent an email to Higgins and Bohner, among others, citing his awareness of the SRS test market plan, and stating that he was now having second thoughts. See G. Mem. 8. Thus, the evidence shows that no later than May 2002, Huggins, Higgin and Bohner were aware of, and involved in, the process of approving the test market for SRS in the spine. See, e.g., G. Mem. 32 and 8; 9, time line of test market approvals, created May 31, 2002 by Norian XR product manager Josi Hamilton.[27]

Nonetheless, despite the consultant's well-founded concerns and Huggins' resultant second thoughts; notwithstanding the growing awareness of the serious risks posed by the Norian products when used in the spine; despite the interpretations and advice given by the FDA and defendant Synthes's own regulatory group; and contrary to the label stating that SRS was not to be mixed with any other substance, defendants Huggins, Higgins and Bohner approved the test market for SRS in the spine, in which employees from the Spine Division Product Development[28] taught spine surgeons how to mix SRS with barium sulfate and use it in

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[27] An entry from defendant Bohner's diary corroborates the time line, showing that a President's Meeting took place on the date listed in the time line. See G. Mem. 80, entry from defendant Bohner's diary for May 22, 2002, while an e-mail exchange between the XR product manager and Bohner, also on May 22, 2002, shows Bohner's awareness of , and apparent agreement to, the planned test market for SRS in the spine. See G. Mem. 10, e-mail chain dated May 22, 2002.

[28] Nisra Thongpreda, Josi Hamilton and Stuart Weikel, who are referred to in the Indictment as Persons 1, 8 and 9, respectively.

surgeries to treat VCFs. Grand jury testimony shows that Thongpreda and Hamilton trained Doctor Barton Sachs (identified in the indictment as Doctor No. 4), while Stuart Weikel trained Doctor Vivek Kushwaha and others. Documents and testimony show that this blatantly illegal "test market" went forward during late summer and fall 2002, with the knowledge and approval of defendants Huggins, Higgins and Bohner. See, e.g., G. Mem. 33, memorandum from Nisra Thongpreda to defendants Huggins, Higgins and Bohner on SRS Training, dated June 4, 2002;[29] G. Mem. 34, Powerpoint Presentation for SRS Training.[30]

After they had authorized it, the defendants kept track of the test market for SRS in the spine. Its progress was discussed at a management meeting in September 2002, attended by defendants Huggins, Higgins and Bohner. See G. Mem. 35, MRB Meeting Spine Business Plan Review Agenda dated September 17, 2002, p. 2; G. Mem. 36, Power Point Presentation on

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[29] Thongpreda sent this memorandum along with a binder to defendant Huggins "containing the training and education information for our test market sites." The memorandum is titled "Synthes Spine Cavity Creation System and SRS Training." She explained that "[a]ll selected test market sites are required to complete this training." The memo outlines the training as including power point presentation on "vertebral compression fractures[,] Cavity Creation System[,] Norian SRS[,] Norian SRS with Barium Sulfate." She asks Huggins to "[p]lease let me know if your require any additional information." Defendants Higgins and Bohner are copied on the memorandum. G. Mem. 33. This memorandum shows that from its inception, the SRS test market was designed to require Synthes personnel to train surgeons to mix the SRS with barium sulfate – as opposed to surgeons mixing the two on their own, the false statement made to the FDA investigator during the inspection. See Indictment Overt Acts 35 and 39; Counts Four and Seven.

[30] The power point contains slides on VCFs, the differences between vertebroplasty and kyphoplasty surgeries, the history of vertebroplasty, competitors' instrument systems, disadvantages of competitors' systems, and disadvantages of PMMA. The power point refers to the Synthes System of instruments and biological implant. (Another version of the power point, used to train at least one surgeon, refers to the Synthes "complete system of instruments and biological implant.") The only use discussed is treatment of VCFs. It does not contain any reference to the warning on the SRS label that SRS is not to be mixed with anything else. The power point also does not refer to the University of Washington pilot studies. It does discuss how to create a cavity in bone and inject the SRS with barium sulfate added. G. Mem. 34.

Test Market for SRS in the Spine given at September 2002 MRB Meeting.

The September 2002 management meeting took place just as the Phase I surgeries were beginning, and two months before the XR Premarket Notification. The minutes of this meeting show that defendants Huggins, Higgins and Bohner all attended (p. 1). The minutes list vertebroplasty as one of the "Key Development Projects." The minutes state in part: (1) "Josi Hamilton presented a project update. . ."; (2) "Josi presented results from a set of animal studies on the XR formulation versus PMMA completed by product development"; (3) there was a discussion that "Test Markets began in September 2002. The test market involves use of the cavity creation instruments and Norian SRS (if desired). Test market participants to publish a case series discussing the Synthes system and the associated clinical results"; (4) "Hansjorg Wyss inquired about the test market set up and how surgeons, who are interested in the product, were to be trained"; and (5) "Several additional studies to be completed by Harborview in Seattle." Clearly, these minutes undercut any suggestion by Huggins, Higgins or Bohner that as of September 2002, they did not know about the test market for SRS in the spine.

The power point presentation given at the September 2002 management meeting discusses the Cavity Creation/SRS test market, that a case had occurred and another was scheduled for the following week, and includes slides showing SRS and SRS-R (later cleared as XR) in the spine from the Texas Back Institute laboratory. The next slide, in the context of the test market, refers to "gather clinical feedback on filler material" and "gathering information of material options in treating VCFs," and "Clinical publication – case series from all sites

published in journal."[31] Following a discussion of potential revenue, there is a slide that chronicles in five bullet points the regulatory history/plan. The second bullet point says: "**May 2002 – FDA conference call discussion XR submission requirements.**" (emphasis added). A later slide refers to competitive pressures, including that Orthovita received FDA approval to conduct a pilot study in the United States for use of CORTOSS in vertebroplasty.[32] In short, this power point further evidences that defendants Huggins, Higgins and Bohner were well aware of the SRS test market in the spine, as well as the safety issues and the discussions with the FDA that had occurred in May 2002.

The results of the test market for SRS in the spine were also discussed later at the July 18, 2003 Safety Meeting and in the Safety Meeting materials, Exhibits 38-42 and 37, see pp. 15-18 above, and 75-78 below. In the Safety Meeting materials the SRS test market surgeries were called "Phase I" of the Norian XR test market.

Finally, at the May-June 2004 FDA inspection, the investigator for FDA asked defendant Bohner whether he knew of a vertebroplasty test market for SRS, and Bohner responded that he did not. G. Mem. 79, p. 117; Indictment, Overt Act 38, Count Six. Bohner stated further that to the best of his knowledge, a vertebroplasty test market for SRS was not discussed at a President's Meeting, when his own diary entries would, at the very least, call that

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[31] This was what the CEO had directed at the November 2001 management meeting, see G. Mem. 5, stating that instead of Synthes pursuing an IDE study, it would instead "get a few sites to perform 60-80 surgeries and help them publish their clinical results."

[32] CORTOSS is not calcium phosphate and, unlike Norian, does not mimic cancellous bone (the spongy bone marrow making up the interior of the vertebral body); rather, it is a composite that mimics cortical bone (the very hard bone on the outside).

into question. G. Mem. 79, id.; G. Mem. 80.[33] Bohner also told the FDA investigator that the 34 test market cases discussed at the July 18, 2003 Safety Meeting involved only data that Synthes had collected from what surgeons were doing on their own, rather than a test market conducted by Synthes, although Bohner did allow that the Safety Meeting materials stating that "two sites were selected to participate" seemed to contradict his understanding. G. Mem. 79, p. 118. The false statements Bohner made to the FDA in 2004 show that Bohner knew back in 2002 that the SRS test market was unlawful. If Bohner had not known that the SRS test market was unlawful back in 2002, he would not have lied about it to the FDA during the 2004 inspection.

The evidence summarized above (pp. 33 through 40) shows that defendants Higgins and Bohner (as well as Huggins) knew about the nature of the test market for SRS in the spine, and they recognized that the test market for SRS in the spine violated the law because it violated the SRS label's ban on mixing. Their objections to paragraph 28 should be rejected.

9. Paragraph 29 of the Presentence Reports

This paragraph recounts the clearance of SRS. It states that on December 20, 2001, Synthes obtained from the FDA 510(k) clearance for SRS as a general bone filler, with a label stating that SRS was intended to fill only bony voids that were "not intrinsic to the stability

[33] An entry from Bohner's diary corroborates the time line, showing that there was a President's Meeting on the date stated in the time line. Compare G. Mem. 80, entry from Bohner's diary for May 22, 2002, with G. Mem. 9, time line. An email exchange between the XR product manager and Bohner, also on May 22, 2002, shows Bohner's awareness of, and apparent agreement to, the planned test market for SRS in the spine. See G. Mem. 10, e-mail chain dated May 22, 2002. Another Bohner diary entry, for May 27, 2004 – during the inspection and more than two weeks before his interview by the FDA investigator – states "FDA daily wrap up . . . MH e-mail of 5/30/02; President's Meeting of 5/22/02. 'We're so consistently bad (sloppy) that it's good' !!" Bohner seems to say that Synthes management did not document what happened at the May 22, 2002 President's Meeting [at which the time line states that the test market for SRS in the spine was discussed], and that this is a good thing. G. Mem. 80, Bohner diary entry for May 27, 2004.

of the bony structure" in the extremities, spine and pelvis, and further warning that SRS was not to be mixed with any other substance. The paragraph continues that Synthes never told the FDA that it intended to market SRS for any load-bearing spine use such as treating VCFs.

Defendant Bohner objects to this paragraph, because it "fails to explain that in its 510(k) application, Synthes proposed labeling that described the intended use of SRS in general terms and included use in the 'spine.' It is lawful to seek a general regulatory clearance from the FDA and later apply for specific indications for use." Bohner Obj. p. 3.

Defendant Higgins objects to this paragraph "to the extent that it wrongly suggests he intended to mislead the FDA, or that he was aware that any other Synthes employee had such intent." Higgins Obj. p. 3.

Similarly, defendant Huggins objects to this paragraph, among others, because it "fails to identify the fact that Mr. Huggins did not communicate with the FDA himself during the period at issue." Huggins Obj. p. 12.

While the government agrees that neither Higgins nor Huggins personally submitted the 510(k) for SRS, paragraph 29 does not say that either defendant did make the 510(k) submission himself, so this objection should be rejected. However, as early as November 1999, defendant Higgins did note to Regulatory the Spine Division's interest in the bone void filler clearance – despite the fact that SRS would be sold by the Trauma Division, not Spine – saying "[i]t sure would be great to have SRS approved for us in bony voids including the extremities, spine and pelvis." Exhibit 2, attached. But even assuming that neither Huggins nor Higgins intended to mislead the FDA with respect to the SRS 510(k) submission, or was aware that other Synthes employees so intended, both took advantage of that submission later. It was a

stepping stone on the way to clearance of XR with the word "spine" in the label. And both Huggins and Higgins knew that the only way that SRS could be approved by the FDA for treatment of VCFs was via the long form of approval, an IDE and a PMA. Both were present at the November 2001 meeting at which the CEO had decided that, instead of Synthes pursuing an IDE study as Higgins suggested, it would instead "get a few sites to perform 60-80 surgeries and help them publish their clinical results." G. Mem. 5. Despite their knowledge of the FDA's stance, the SRS 510(k) submission went forward. If instead, Huggins, Higgins or someone else at Synthes had told the FDA that the company intended to market an extra-radiopaque version of SRS for surgeries to treat VCFs, then the company would have been told in December 2001, instead of a few months later, in May 2002, what Norian and Synthes had already been advised: that the FDA had serious concerns about the use of bone void fillers in the spine, and approval of a bone void filler for that intended use would require an IDE and a PMA.

Similarly, Bohner's description of the labeling Synthes proposed to the FDA for SRS is misleading, when considered against the backdrop of the information that he and others at Synthes had received since 1999 about the FDA's concern over use of bone void fillers in the spine. E.g., G. Mem. 12. As stated above, Bohner, Huggins and Higgins all knew, by November 2001 at the very latest, that the 510(k) labeling proposed by Synthes and accepted by the FDA did not permit Synthes to market SRS for weight-bearing indications, especially in the spine. This is because they had been made aware, by the IDE proposal reviewed by Bohner and seen by Huggins and Higgins at the November 2001 management meeting, that Synthes could gain the FDA's permission to market SRS for surgeries to treat VCFs, only by means of an IDE and a PMA, the long form of approval. Synthes could, and did, hide its true intended use of SRS from

the FDA, then take its chances on whether it would get caught. But this put the company at significant risk, particularly because the company had been told by the FDA that the FDA had serious concerns about use of bone void fillers in the spine. G. Mem. 12; and later G. Mem. 13. So not only was this an off-label use but this was off-label use in the area about which the FDA had expressed serious concerns.

Moreover, while in some circumstances it may be lawful to seek a general regulatory clearance from the FDA and later apply for specific indications for use, the clearance Synthes sought and received for SRS, while a clearance as a general bone void filler, was a very narrow indication, that did not include weight-bearing indications in the spine or anywhere else. In seeking 510(k) clearance, a company is informing the FDA that it is planning to market the product for a certain indication. The FDA's role in the clearance process is to determine whether the proposed product is "substantially equivalent" to the predicate, and to voice objections if any changes from the predicate – either in technological characteristics or intended use – could substantially affect the safety or effectiveness of the device. With SRS, Synthes told the FDA that it was planning to market SRS for a certain indication, i.e., as a bone void filler to fill only certain (but not all) voids in the extremities, spine and pelvis. SRS was essentially a putty used to plug holes, and could not be used in weight-bearing indications. The label language, restricting SRS's use to filling only those bony voids that are not intrinsic to the stability of the structure, meant that SRS was not to bear a load. Using SRS to provide stability to a fractured vertebral body means that it will bear a load. That means that such use is intrinsic to the stability

of the vertebra.[34] This was consistent with the mechanical properties of SRS, which was strong in compressive strength, but weak in torsional and shear strength. At bottom, defendants Huggins, Higgins and Bohner well understood that the SRS (and XR) indications statement did not allow Synthes to promote SRS for treatment of VCFs, as this is exactly what Synthes told its physician customers in its February 2004 "dear surgeon" letters – signed by defendant Huggins – when it stopped the test markets. G.Mem. 76.

10. Paragraph 30 of the Presentence Reports

This paragraph states that by May 2002, Synthes and Norian had engaged in multiple conversations with the FDA about CRS and SRS. As a result of those conversations, starting as early as 1999, Synthes and Norian were aware of the FDA's concerns with the products and, in particular, that the FDA was concerned about their use in the vertebral bodies.

Defendant Huggins objects to this paragraph, among others, because it "fails to identify the fact that Mr. Huggins did not communicate with the FDA himself during the period at issue." Huggins Obj. p. 12.

Once again, this objection is meritless. While it is true that so far as the government's investigation shows, Huggins (unlike Bohner, see G. Mem. 12)[35] did not have

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[34] Although the indication statement on the SRS label – that SRS is intended to fill only those bony voids that are "not intrinsic to the stability of the bony structure" in the extremities, spine and pelvis – is hardly a model of clarity, it is also true that the vertebral bodies, which make up the front two out of the three columns of the spine, bear 80% of the load in the spine, with the back column bearing 20%. Indictment paragraph 26. Therefore, injecting bone void filler or bone cement into the vertebral body in order to stabilize it, as is done to treat VCFs, is intrinsic to the stability of the vertebra. It would also be intrinsic to the stability of the spine.

[35] G. Mem. 12 is the minutes of a telephone conference call held July 8, 1999 between the (continued...)

direct contact with the FDA concerning the Norian cements prior to the May-June 2004 inspection, he did have notice of the FDA's safety concerns with use of bone void fillers in the spine. For example, he received G. Mem. 17, an email dated August 23, 2000 from Group Manager of Synthes Regulatory Sharp, to defendants Higgins and Bohner, when Bohner forwarded it to him that same day. After stating that Regulatory was unaware of a planned "test market" for SRS in the spine, that email continues:

> We cannot promote the use of SRS for unapproved indications, and this is especially true for use in the spine, where FDA has previously made it clear to Norian that any intraspinal use would require additional approval.

G. Mem. 17.

Defendant Higgins also received notice through the FDA's statements to another company, in the form of a Warning Letter to a competitor, showing the FDA's concerns about claims for general orthopedic devices for use in the spine. See, e.g., G. Mem. 20, e-mail from Sharp to defendant Higgins and others, attaching Kyphon Warning Letter, dated December 4, 2000. All three received notice from the FDA's public pronouncements, or WebAlerts, publicizing complications that had been reported related to vertebroplasty-type surgeries to treat VCFs. One WebAlert in October 2002, updated later, warned that the reported complications were related to the leakage of PMMA during surgeries to treat VCFs. See G. Mem. 21, FDA Public Health Web Notification ("WebAlert") dated October 31, 2002; G. Mem. 22, e-mail from defendant Huggins to defendants Higgins and Bohner and others, attaching updated WebAlert

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[35](...continued)
FDA and Norian and Synthes employees including defendant Bohner. The minutes report that during the meeting, an FDA representative stated that "[s]pinal applications are hot buttons: FDA has little information on bone void filler use in the spine. Such use will almost definitely require a PMA."

dated April 4, 2003.

11. Paragraph 31 of the Presentence Reports

This paragraph details a May 8, 2002 conference call between the FDA and Synthes and Norian representatives. It recounts that on May 8, 2002, Synthes and Norian had a telephone conference call with the FDA concerning the new SRS plus barium sulfate (the product eventually cleared as XR). During the call, the FDA stated that it was concerned about the imprecision in the current indication for use, and that as a part of their practice of medicine, surgeons were using bone void fillers in the spine for load-bearing indications. The FDA asked that Synthes and Norian provide additional labeling for XR that specified that spinal load-bearing indications, such as vertebroplasty, were not included in the current indication for use. Synthes and Norian advised the FDA that XR would not be promoted for use in vertebroplasty or other load-bearing indications without the appropriate regulatory authority. However, Synthes and Norian also expressed their belief that such labeling would create an uneven playing field, as no other manufacturers of other bone void fillers had such labeling. Nevertheless, the FDA continued to insist on such labeling until Synthes submitted the warning against VCF use that became part of the Norian XR label.

Once again, defendant Huggins objects to this paragraph, because it "fails to identify the fact that Mr. Huggins did not communicate with the FDA himself during the period at issue." Huggins Obj. p. 12.

Bohner objects to this paragraph and paragraph 32, stating that he "did not participate in the May 2002 conference call. Nor did he attend the meeting in December 2002 where Synthes employes allegedly expressed concern about company-sponsored educational

events for vertebroplasty." Bohner Obj. p. 4.

As to the telephone conference with the FDA on May 8, 2002, the government's investigation shows that neither Huggins, Higgins or Bohner was present. Indeed, since paragraph 31 does not state that any of them were present, these objections are meritless. And while both Higgins and Bohner were copied on the minutes of the May 8, 2002 meeting, G. Mem. 13,[36] Huggins' name does not appear there. However, again, all three defendants had notice of the May 8 conference call with the FDA. First, because the minutes of the May 8 conference call with the FDA were attached to the subsequent 510(k) submission to the FDA for Norian XR. Second, because the power point presentation given at the management meeting in September 2002, which Huggins attended, refers to the May 8 conference call, stating "May 2002 – FDA conference call discussion XR submission requirements." G. Mem. 36.

In addition, Bohner (like Higgins) received the minutes of the May 8, 2002 conference call and so learned of the concerns expressed by the FDA representatives during that call; the promise made on behalf of Synthes by Sands, who reported to Bohner, that the companies would not promote XR for vertebroplasty or other load-bearing indications in the spine without the proper regulatory approval; and the additional labeling that the FDA sought for XR, specifying that spinal load-bearing indications, such as vertebroplasty, were not included in the current indication for use. What constituted proper regulatory approval to promote XR for vertebroplasty, as Sands had already told all three defendants starting in November 2001, was

[36] In addition, Barry Sands, the Synthes Spine Regulatory representative who promised FDA that Synthes would not promote XR for use in vertebroplasty or other load-bearing indications without the appropriate regulatory authority, testified in grand jury that he hand-carried copies of the minutes to the offices of defendant Higgins, among others, and told Bohner and Higgins, as well as others in the Spine Division, what was discussed on the call.

the long form of approval, an IDE and PMA. But this was the form of approval that the company had already rejected at the direction of its CEO, in favor of the illegal SRS "test market." So this was information all three already had. It was not news to them.

12. Paragraph 32 of the Presentence Reports

This paragraph recounts that after the May 2002 conference call between Synthes and Norian, the Synthes and Norian representative understood that the only way that Synthes could receive approval for load-bearing spine indications such as vertebroplasty was through an IDE and a PMA application. Prior to May 2002, this same representative and others had communicated this fact to others higher up in Synthes' management. In addition, by May 2002, Synthes' own regulatory employees had also given Synthes notice that promoting use of SRS to treat VCFs was illegal. Other Synthes employees, from other departments, echoed and emphasized this same concern in December 2002, suggesting that the opinion of legal counsel should be sought on the question if there was any doubt about the promotion of XR for use in vertebroplasty or other load-bearing indications. The paragraph concludes that counsel was not consulted until after the third patient death in January 2004.

Defendant Bohner objects to paragraph 32 as "misleading in that it omits the evidence showing confusion about the SRS label." He selects bits of grand jury testimony by two surgeons,[37] to the effect that at the time of his grand jury testimony (2008), each surgeon

[37] The first surgeon quoted is Dr. Helfet, a trauma surgeon who was a member of Synthes' board of directors, and who attended the Safety Meeting in July 2003. Helfet testified that he had never read the SRS label until "all this came up" (i.e., the investigation), but that his own (recent, therefore irrelevant) interpretation of the SRS label was that it was and remains confusing because if you don't believe that you need bony stability, you can use SRS to fill any bony void in the skeleton, including the spine. Although Helfet had previously stated in a proffer interview that the words "not intrinsic to

(continued...)

believed that the SRS indication statement was confusing. For the reasons stated in connection with defendant Huggins' general objection on the same point, see pp. 5-10, above, this objection is equally meritless. When the surgeons' testimony is read in context, it does not support the inference Bohner asks the Court to draw: that because, in 2008, two surgeons read the SRS indication statement and found it confusing, anyone at Synthes had been confused about that indication statement back in 2002, after the May 2002 conference call with the FDA. Bohner has presented no evidence that anyone at Synthes was confused by the SRS indication statement during the relevant period, nor could he. After the third death, Synthes sent "dear surgeon" letters to spine surgeons, admitting that use of Norian XR to treat VCFs was off-label but

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[37](...continued)
stability of the bony structure" on the label meant that there was no proper use of SRS in the spine, in the grand jury Helfet testified that he did not recollect making that statement.

The other surgeon Bohner quotes is Dr. Nottingham, the spine surgeon identified in the Indictment as Doctor No. 5. On September 19, 2003, when Dr. Nottingham used Norian XR in a surgery using Cavity Creation instruments to treat VCFs, his patient died on the operating table after suffering a hypotensive episode ("the second death"). Dr. Nottingham noted a cement leak, believed that it was the cause of the episode, and could not rule out Norian XR as a cause of the second death. Indictment ¶ 70.

In grand jury, Dr. Nottingham testified that his Synthes sales representative had introduced the idea of his using XR in a vertebroplasty surgery. He testified that the sales representative gave him the impression that the Norian product was FDA approved for use in vertebroplasty. Neither the sales representative nor Dr. Nottingham's partner, Dr. Hieu Ball – who had been trained by Synthes as part of the XR test market – ever mentioned the FDA warning label, the test market, the adverse events, or the University of Washington pilot studies. Dr. Nottingham testified further that in September 2003, he did not know he was part of Synthes's test market, or that Synthes was collecting safety and efficacy data from his surgery. Dr. Nottingham testified that during attempts to resuscitate the patient, one of the OR nurses read and summarized for him the XR label. It was then that Nottingham learned for the first time that Norian XR did not have the FDA approvals he was led to believe it had. However, in grand jury he testified that he still does not understand the "only for bony voids or defects that are not intrinsic to the stability of the bony structure" portion of the indication statement. Nottingham commented that this did not make any sense to him because the purpose of bone is to provide structure and stability. He testified that the warning bullet was explicit and clear, but that he thought he had not read it until the government showed it to him. He testified that if he had seen the warning bullet before September 19, 2003, he would not have used XR during the surgery.

explaining that such use was off-label because it was "intrinsic to the stability of the bony structure," and remaining silent about the warning bullet. The "dear surgeon" letters were signed by defendant Huggins, and defendants Walsh, Bohner and Higgins were involved in the drafting process. The "dear surgeon" letters show that none of these four defendants were confused by the SRS indication statement.

13. Paragraph 34 of the Presentence Reports

This paragraph recounts five events that happened before or during the indictment period showing that Synthes and Norian were increasingly on notice that the Norian bone void fillers might pose serious risks if used in the spine in humans. These events put the individual defendants on notice as well. Paragraph ¶ 34A-E is set out in the footnote below.[38]

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[38] Two adverse hypotensive events occurred in February 2001 when a spine surgeon, identified in the indictment as Doctor No. 1, used CRS off-label in two kyphoplasty surgeries to treat VCFs in two patients (each time, the CRS had been carried to the operating room by a Synthes sales representative, who was present in the operating room during the surgeries). These were two of the first VCF surgeries with a Norian cement in the United States. Both patients survived but one had to spend 3 to 4 days in the hospital's intensive care unit. Synthes learned that Doctor No, 1had previously performed about 50 VCF surgeries with PMMA without incident. Synthes filed Medical Device Reports ("MDRs") on the two Doctor No. 1 hypotensive events. Documents reflect that subordinates informed Huggins of the two Doctor No. 1 hypotensive events. Huggins, in turn, directed subordinates to reel in the sales force "ASAP" concerning the use of CRS in VCF surgeries.

At a meeting called by Synthes with surgeons and researchers to try to learn the cause(s) of the Doctor No. 1hypotensive events, one participant, a prominent trauma surgeon from the University of Washington ("UW"), identified in the Indictment as Doctor No. 2, reported that the Norian in its pre-hardened state might be interacting with blood and causing problems. He told Synthes that he believed it was critical that there be a study of the pre-hardened state of Norian before it was used in live patients because, in its pre-hardened state, Norian had the potential to interact with tissues and blood in a way that hardened Norian did not.

In November 2001, at the annual Spine sales meeting, Synthes invited Doctor No. 2 to speak to the Spine sales force about surgeries to treat VCFs. Doctor No. 2 discussed the serious complications of vertebroplasty-type surgeries to treat VCFs, including leakage of the cement into the venous system, which could cause pulmonary embolism and death.

(continued...)

In the current objections, only defendant Bohner takes issue with ¶ 34. In addition, some earlier objections by certain defendants to ¶ 34 are included in the PSRs, at footnote 8 to that paragraph. The government responds to all of those objections here.

In earlier objections, a defendant or defendants objected to ¶ 34 because it "failed to point out that surgeries on elderly and often infirm patients, such as those that spine surgeons perform to relieve the intense pain of [VCFs], have a higher risk than surgeries performed on younger, healthier patients. Consequently, if doctors choose to perform such procedures, there would always be a possibility of adverse events." The objecting defendant(s) argued that "the documents reflect that this subject was discussed by Synthes at meetings, and it was the reason why Synthes chose to proceed slowly and cautiously with the release of a product, Norian XR, that doctors would likely choose to use in such situations."

This apology for the test markets goes a long way toward proving the government's theory of the case. Why would a company that has gone to the trouble and expense of developing a new product and securing FDA approval for it do anything other than put the product on the open market? The reason: the intended market for the product was for an

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[38](...continued)

In April 2002, another surgeon published an article in Spine Journal of Bone and Joint Science concerning the death of his patient during spinal screw augmentation surgery with CRS.

In May and June 2002, Doctor No. 2 and his partner, identified in the indictment asDoctor No. 3, told Synthes that they had performed pilot studies at the University of Washington with SRS which showed that even small amounts of SRS could generate formation of large volumes of blood clot if SRS escaped from bone into the venous circulation (the "pilot studies"). The pilot studies showed that the calcium contained in SRS had a unique interaction with human blood, providing both a surface on which clot could form and a chemical stimulus to clot formation. The pilot studies further showed dramatic clotting of a pig's lung veins following injection of SRS. The surgeons also reported some of their findings from their pilot studies with SRS to the FDA via an MDR.

unapproved use, i.e., in surgeries to treat VCFs. Synthes recognized early on that there were two possible solutions to this problem: (1) the legal solution, which was to secure FDA approval of XR for use in vertebroplasties to treat VCFs after an IDE to investigate the safety and efficacy of the product, and (2) the illegal solution, which was to promote XR for use in VCFs through a limited test market during which Synthes would evaluate the safety and efficacy of the product in unsupervised clinical trials and judge their success according to its own standards. Acting through these defendants, Synthes chose the illegal solution, got caught, and now, in defense of its conduct, seeks credit for not having attempted an unauthorized clinical trial on a larger scale.

As detailed in here and elsewhere, Synthes's limited test markets were not slow, or cautious, or careful, or motivated by patient safety. In deciding to embark on test markets for SRS and XR in VCF surgeries, these defendants ignored alarming study results and patient outcomes (including deaths) and concealed them from the surgeons that they invited to use the products. These defendants also disregarded clear statements from the FDA that use in surgeries to treat VCFs was off-label and warnings from both Synthes employees and outside surgeons that this conduct was illegal.

A defendant or defendants also objected earlier to alleged omissions in ¶ 34A, which discusses the two (non-fatal) adverse hypotensive episodes[39] that occurred in February 2001, when Dr. Delamarter (Doctor No.1) used CRS[40] off-label in two kyphoplasty surgeries to treat VCFs in two elderly patients. These were two of the first VCF surgeries with a Norian cement in the United States, and each time, the CRS had been hand-carried into the operating

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[39] Serious drops in blood pressure.

[40] CRS was and is indicated only for cranial use.

room by a Synthes employee, who was present in the OR during the surgeries.

As the PSR writer noted in response to the objection, it is correct that: both surgeries took place on the same day; each patient had other medical problems; and a Synthes Regulatory employee spoke with Dr. No. 1 afterwards and informed him that use of CRS in surgeries to treat VCFs was off-label. However, these facts, while true, are largely irrelevant. The target population for surgeries to treat VCFs is overwhelmingly elderly and frail, and not surprisingly, they often have other medical problems, G. Mem. 1, 19. And speaking with the surgeon after the surgery to inform him that it was off-label does not answer the question of why the Synthes employee (a sales consultant from the Trauma Division) had hand-carried the CRS into the surgery of a spine surgeon in the first place.[41]

Defendant Bohner objects to paragraph 34A that he "had no advance notice of [Dr. Delamarter's] surgery or that a sales consultant would be present during the surgery." Bohner Obj. p. 4. There were in fact two surgeries, on the same day, and the Synthes sales consultant was present at both, but since paragraph 34A does not state that Bohner had advance notice that this spine surgeon would use CRS to treat two patients' VCFs, or that he knew in advance that a Trauma Division sales representative would be present, this aspect of his objection should be rejected.

Also in connection with ¶ 34A, Bohner objects further that

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[41] It would appear that someone higher than the sales consultant had to have known that Dr. Delamarter was going to use CRS off-label, because that consultant would not have known Dr. Delamarter, Dr. Delamarter would not have known her, and he would have had no reason to contact her. It stands to reason that the sales consultant was directed to attend Dr. Delamarter's two surgeries because she had had training in mixing the CRS, whereas at this time, the Spine sales representatives had not.

> [t]his paragraph fails to state that in response to these events the company sent a strongly worded message to the sales force that Synthes cannot promote and does not support off-label use of the CRS and SRS. The message instructed sales consultants not to be present during cases involving off-label uses of Norian products, and warned that disciplinary action might be imposed if consultants failed to comply with this instruction.

Bohner Obj. pp. 4-5.

The government agrees that, after CRS was used in the two kyphoplasty surgeries to treat VCFs, and the adverse events occurred, defendant Huggins sent a message to the sales force. However, Huggins' message was anything but strongly worded. Emails show that subordinates, including Bohner, informed Huggins of the two hypotensive events,[42] and that in response Huggins directed subordinates to reel in the sales force "ASAP" concerning the use of CRS in VCF surgeries. See G. Mem. 25; 26, Huggins email to Bohner and another manager dated March 16, 2001. These emails show that Huggins and Bohner were aware of their duty to avoid off-label marketing. However, despite their knowledge of that duty, the actual message that Huggins sent the sales force was confusing at best. It gave no details of the surgeries, failing to mention that the two hypotensive episodes had happened during two kyphoplasty surgeries to treat VCFs. This left the sales force in the dark as to what procedures surgeons were performing that Synthes management believed were outside of the labels of SRS and CRS. See G. Mem. 52, p. 2.

Paragraph 34B recounts that, after these two adverse events, Synthes called a meeting of expert surgeons to try to determine the cause of the adverse events, the Norian for

[42] Defendant Higgins learned of them no later than March 1, 2001, and defendant Bohner learned of them no later than March 16, 2001. See Exhibit 25.

Spine Indications Focus Group ("Spine Focus Group").[43] G. Mem. 27, meeting materials. One participant, Dr. Sohail Mirza, a prominent trauma surgeon from the University of Washington, identified in the Indictment as Doctor No. 2, reported that the Norian in its pre-hardened state might be interacting with blood and causing problems. He told Synthes that he believed it was critical that there be a study of the pre-hardened state of Norian before it was used in live patients because, in its pre-hardened state, Norian had the potential to interact with tissues and blood in a way that hardened Norian did not.

A defendant previously objected to ¶ 34B, describing the Spine Focus Group meeting, saying that the paragraph should note that "the surgeons attending could not identify a link between the adverse events and CRS, which is reflected in the notes of the meeting." To the extent that this objection references what Higgins and the other participants decided to do next, it is inaccurate. The taker of those notes has testified in grand jury that at the conclusion of the meeting, it was decided that the issue of how pre-hardened Norian acted in the blood should be further investigated, as indeed it was. The pilot studies were undertaken to answer this question.

Defendant Bohner raises a similar objection to ¶ 34B, that it "fails to state that the surgeons and researchers who attended the meeting could not determine the cause of the Dr. No. 1 hypotensive events." This is true but irrelevant for the reasons stated above.

A defendant objected to ¶ 34E, concerning the pilot studies conducted at the University of Washington on human blood and on pigs. Those pilot studies began in April 2002. Researchers, including Drs. Chapman and Mirza, added human blood to powdered Norian in a test tube and added liquid Norian to human blood in a test tube. The results suggested that a

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[43] Defendant Higgins was responsible for calling the Spine Focus Group meeting.

small amount of Norian would produce a large amount of clot. That clot could result in a pulmonary embolism if it traveled to the lungs. The researchers then injected 2 cc's of liquid Norian into a full-size pig's inferior vena cava, and the pig died within 30 seconds. A Synthes sales consultant was present at these pilot studies.

Doctor Chapman emailed the results and his concerns to defendant Higgins and others at Synthes a few days later. He wrote that there was definitely a need for further investigation. Given the results of the pilot studies, and the adverse events in Dr. Delamarter's, Chapman's and Mirza's own patients, on June 28, 2002, the researchers submitted to Synthes, copying Higgins, a grant proposal listing six separate safety studies with Norian SRS that they wanted to conduct. G. Mem. 31. They stated that they had performed pilot studies with Norian SRS which showed that even small amounts of SRS could generate formation of large volumes of blood clot if SRS escaped from bone into the venous circulation. The pilot studies on human blood in test tubes showed that the calcium contained in the unique formulation of Norian SRS had a unique interaction with blood, providing both a surface on which clot could form and a chemical stimulus to clot formation. The pilot studies further showed dramatic clotting of a pig's lung veins – consistent with the human blood tests – following injection of a small amount of SRS.[44] In that same mailing, they expressed their concerns about Norian being a potential thrombogenic agent, and stated that this should be reported to the FDA because it might pose liability risks for Synthes. They included an MDR to be sent to the FDA. G. Mem. 31. So far as

[44] By contrast, and as noted in G. Mem. 31, any risk of embolus that PMMA may pose comes not from how its components interact with blood – PMMA is not known to cause or accelerate blood clots – but from liquid PMMA escaping into the venous system and only then hardening (polymerizing) into a bolus that can obstruct blood flow.

the government's investigation determined, these initial findings were never undercut by any subsequent research.

The defendants' objections, set out in footnote 8, are three: (1) that the PSR "characterized the study's findings"; (2) that the pilot studies included a lethal dose (LD50) study on pigs "not intended to simulate any clinical procedure that would be performed on humans, nor was it designed to evaluate the risks associated with such procedure" and (3) that after additional animal studies, for which Synthes provided some funding, "the doctors felt there was not enough information available at the time to draw specific conclusions, but Dr. No. 3 stated that Norian, if used properly, was a safe and valuable device."

The first two objections miss the central point. Obviously, the pilot studies were not intended to simulate surgeries to treat VCFs in humans; they were meant to investigate whether Norian could cause blood clots by accelerating the coagulation of blood. G. Mem. 31. The further tests that the pilot study researchers asked Synthes to fund were to "explore the safety of Norian as a biomaterial for vertebroplasty." G. Mem. 31, p. 6-7. The results of the pilot studies, stated above, p. 55, have never been disproven. Doctors Mirza and Chapman, who conducted the pilot studies, so testified in grand jury.

The pilot study results raised a real question whether Norian would cause blood clots if it escaped into the venous system. Leakage was a real concern during vertebroplasty, as many blood vessels are near the spine. Sometimes pilot studies can be definitive. Pilot studies can raise a safety issue so serious that the product should not be marketed until the pilot study conclusion is disproved. In this case, where the pilot studies showed that Norian appeared to accelerate blood clotting, which could cause pulmonary embolism and death, it was only prudent

for Synthes to investigate these findings further before testing Norian on humans. But instead, Synthes pushed forward with the test market for SRS in the spine, and later, the XR test market. This was not only illegal, because it evaded the FDA's oversight of clinical trials, but also unethical in view of the risks to patients.

The third objection is misleading. Following the FDA inspection, in June 2004, at the request of defendant Huggins, Dr. Chapman wrote a letter to Synthes stating, among other things, that Norian, when used in a dry surgical field, remains a safe and valuable device. The objection fails to note what amounts to a huge caveat, as the spine is definitely not a dry surgical field. In any event, as far as the government is aware, Norian was never tested in a dry surgical field. Moreover, when Dr. Chapman wrote the letter to Synthes at Huggins' request, after the FDA inspection, he had received funds directly from Synthes to conduct follow-up studies of Norian, and had also obtained on behalf of his university, a $2,000,000 endowment from the CEO of Synthes.

14. Paragraph 35 of the Presentence Reports

Paragraph 35 details how, at the end of May 2002, these three defendants approved the test market for SRS in the spine and how, during that test market, Synthes employees created a recipe for mixing SRS with barium sulfate to make it more radiopaque; distributed that recipe to spine surgeons; trained spine surgeons how to use SRS that had been mixed with barium sulfate in surgeries to treat VCFs; attended VCF surgeries; and gathered safety and efficacy information on the VCF surgeries. The test market surgeries took place during late summer through winter 2002, and were the subject of Synthes management meetings in fall 2002 and July 2003, including the Safety Meeting, where they were called "Phase I" of the

Norian XR test market. The test market for SRS in the spine is described at ¶ 35 of the PSR, at pp. 30-35, above, and in the Indictment, ¶ 82, Overt Acts 1, 2.

Not surprisingly, defendants Huggins, Higgins and Bohner all object to ¶ 35. Bohner objects to the entire paragraph "insofar as it suggests that he engaged in intentional wrongdoing." Huggins objects that

> [t]he PSR incorrectly asserts that Mr. Huggins and others engaged in improper conduct in mid-2002 with respect to Norian SRS because they were aware that doctors were using barium sulfate (the radiopaque agent useful for x-rays) despite the label's statement that Norian SRS was not to be mixed with any other substance. To put the matter in perspective, the FDA *itself* allowed the mixture of barium sulfate with the Norian bone cement later in the same year (a fact not mentioned in the PSR). The PSR cites a May 2002 email written by Mr. Huggins, in which he stated that he was concerned about the use of Norian SRS out of scope, as if it were evidence of impropriety. To the contrary, it is one of many exculpatory examples of Mr. Huggins' caution and commitment to safety and procedural regularity.

Huggins Obj. p. 9 (emphasis in original). Higgins objects to footnote 10 to ¶ 35, concerning his earlier objection to ¶ 35: Higgins claimed that Synthes decided to "advise the surgeons how to mix [SRS and barium sulfate] properly" in the "interest of patient safety" because Synthes was faced with a "dilemma." According to Higgins, "on their own" surgeons had expressed a strong desire to add barium sulfate to SRS, leaving Synthes with "two perceived alternatives": letting the surgeons mix SRS on their own, with high risks of incorrect mixing (since Norian handles differently than PMMA), and poor outcomes for patients, or advising the surgeons how to mix it. In footnote 10, the PSR writer observed that this "dilemma" appeared to have been self-created, since Synthes had created the market for the off-label use of a more radiopaque version of SRS for VCF surgeries in the first place, in spite of knowledge of the patient risk involved.

In connection with footnote 10, Bohner objects that he did not make the earlier

objection discussed there, that led the PSR writer to describe the so-called dilemma as self-created and the objection as inaccurate and misleading. Bohner states further that he neither approved, directed nor participated in the surgeon interviews in spring and summer 2000 (that culminated in the Vertebroplasty Market Summary, G. Mem. 1). The government agrees that footnote 10 to ¶ 35 should be amended to state that Higgins alone made the earlier objection.[45]

Treating Bohner's objections first, his blanket objection to ¶ 35 "insofar as it suggests that he engaged in intentional wrongdoing", raises a factual issue that the Court must resolve at sentencing: whether Bohner was involved in intentional wrongdoing when he approved and then oversaw the SRS test market for the spine. This objection is closely related to the issue raised by Bohner's objection to ¶ 28 of the PSR, also discussing the test market for SRS in the spine, that is, whether Bohner was aware at the time that it and the later XR test market violated the law. That issue is discussed at pp. 30-35, above. The government submits that the documentary evidence and the grand jury testimony of the Synthes Spine employees, detailed at pp. 30-35 above, as buttressed by Bohner's own statements, both at the time and later, all show that Bohner (as well as Huggins and Higgins) well knew that these test markets were unlawful – the SRS test market because it contravened the label ban on mixing and the XR test market because it was for the unapproved and warned against indication of surgeries to treat VCFs.

Higgins' and Huggins' objections to ¶ 35 also raise factual issues of a different sort that the Court must resolve at sentencing. Their accounts of the SRS test market contradict one another. While Higgins admits that Synthes taught the spine surgeons how to back-table mix

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[45] Bohner reiterates here his earlier objection to ¶ 28, that he did not approve, direct or participate in the market research to spine surgeons referred to in footnote 10 to ¶ 35. As discussed above, this is correct, but Bohner was aware of the market research, at least at its conclusion.

SRS with barium sulfate, and gives an explanation why, Higgins Obj. pp. 3-4, Huggins apparently denies that this happened, arguing that all he did was to be "aware that doctors were using barium sulfate . . . despite the label's statement that Norian SRS was not to be mixed with any other substance." Huggins Obj. p. 9. The documentary and testimonial evidence shows that, as Higgins concedes, the SRS test market for the spine involved Synthes, through its Spine Division employees, teaching the spine surgeons to back-table mix the SRS with barium sulfate, then teaching them to use the resulting mixture in surgeries to treat VCFs. The government submits that this issue should be resolved at sentencing in favor of Higgins' admission that Synthes did teach the surgeon how to mix SRS (though the government disagrees with his fallacious claim that Synthes faced a dilemma, see below).

Huggins' further objection that the SRS test market was permissible – despite the label's prohibition on mixing – because later, in December 2002, the FDA cleared XR, a mixture of calcium phosphate and barium sulfate, is frivolous. The ad-hoc process of back-table mixing, with its inherent lack of precision (despite the recipe that the Spine employees provided), cannot be compared to use of an FDA-cleared product containing a standardized amount of each ingredient. One might just as well say that it is permissible for a doctor may practice medicine before he or she has become licensed, or for a lawyer to practice law before passing the bar, because at some point later, they will obtain the proper credentials.

Huggins' final objection to ¶ 35 is that his May 30, 2002 email to Higgins, Bohner and others, concerning shipment of SRS for spine use and his talk with Dr. Lambert about the SRS test market (G. Mem. 8) is misconstrued by the presentence writer. According to Huggins, this email should properly be understood as exculpatory. He argues that far from evidencing

wrongdoing, this email is "one of many exculpatory examples of [his] caution and commitment to safety and procedural regularity." This is audacious in the extreme. Huggins' email states that:

> There appears to be some shipments being made of Norian for Spine use which we need to discuss. We discussed about the need to perform a real study to test Norian. We shouldn't be sending out product without proper protocols, surgeon sponsors, etc. As you know we have gone through great lengths in SUSA [Trauma Division] to train surgeons on Norian's use. It seems Spine is bypassing the needed blocking and tackling without thinking this all the way through.
>
> In addition, I had a long phone conversation with Dr. Lambert, who is very concerned about the Spine plan. I am now having second thoughts. Please make that shipments are stopped until we can discuss and resolve all the issues.
>
> I will set up a meeting for Monday to discuss.

G. Mem. 8.

This email shows that Huggins (1) knew about the test market for SRS in the spine; (2) knew that shipments were already being made as a part of that test market; (3) knew that there was a "need to perform a real study to test Norian"; (4) had spoken to Dr. Lambert; (5) knew that Dr. Lambert opposed the Spine plan (see G. Mem. 32 for Dr. Lambert's views that because of patient safety reasons, the plan to use SRS with vertebroplasty amounted to human experimentation); (6) was now having second thoughts about the test market because of having spoken to Dr. Lambert; and (7) was directing that shipments be stopped until management could discuss and resolve all the issues. G. Mem. 8.

After this email, more meetings took place. Meetings had already occurred, as outlined in the XR product manager's time line. G. Mem. 9. But despite all that Huggins and the other defendants knew, and after all of the hand-wringing, Huggins directed that this test

market should go forward nonetheless. Huggins' email provides powerful corroboration of the other evidence – including Higgins' admission – that the SRS test market involved teaching the spine surgeons to mix the SRS prior to teaching them to use it in surgeries to treat VCFs, not just being aware that spine surgeons were doing so. It is in no way exculpatory.

Higgins' objection to ¶ 35 demonstrates the fallacy of bifurcation. He presents Synthes as having only two alternatives when in fact other alternatives existed. Synthes was not required to gin up a market for use of SRS in surgeries to treat VCFs, G. Mem. 1, 2, 3, but having done so, it did not face a dilemma – allowing spine surgeons to mix poorly, or assisting them despite the SRS label's proscription against mixing – either.

Higgins overlooks the simple fact that, at any time, Synthes could have obeyed the law. Synthes could have informed the spine surgeons of the University of Washington pilot study results, and cautioned them against off-label use in light of the need for further studies; it could have informed the spine surgeons of Dr. Delamarter's two adverse events in February 2001; it could have issued clear directives to its sales force that the concerning off-label use was in surgeries to treat VCFs; it could have imposed the moratorium on spine use that Dr. Lambert believed was in effect; or it could have done all of those things together. Each of the defendants who now stand before the Court had many opportunities to follow the law and protect patient safety. Instead, through these defendants, Synthes chased the profit that was to be had in treating older persons with VCFs.

15. Paragraph 36 of the Presentence Reports

This paragraph details how, in fall 2002, Synthes submitted to the FDA a Special 510(k) premarket notification for XR requesting clearance for a general bone void filler

indication, listing Norian as the manufacturer, and telling the FDA that XR was substantially equivalent to SRS. Notwithstanding the promise that Synthes and Norian had made during the conference call with the FDA, Synthes made the submission without the language requested by the FDA, that is, without language stating that Norian XR was not intended for load bearing indications such as treating VCFs. Synthes never told the FDA that its true intended use for XR was to market it for load-bearing spine use such as treating VCFs.

Again, defendants Huggins, Higgins and Bohner all object to this paragraph. Bohner objects because he "did not draft or review the company's 510(k) submission for Norian XR", Bohner Obj. p. 5; Huggins objects because it "fails to identify the fact that Mr. Huggins did not communicate with the FDA himself during the period at issue", Huggins Obj. p. 12, and Higgins "to the innuendo that Synthes 'hid its true intended use' for Norian XR from the FDA. Mr. Higgins had no intent to hide anything from the FDA", Higgins Obj. p. 4.

While the government agrees that neither Huggins nor Bohner personally submitted the Special 510(k) for XR, paragraph 36 does not say that either defendant did make that submission himself, so this objection should be rejected.

As to Higgins' objection to the statement that Synthes hid its true intended use for Norian XR from the FDA, and his claim that he had no intent to hid anything from the FDA, the government submits that once more, this raises a factual issue that the Court must resolve at sentencing. The evidence in support of both conclusions – that Synthes hid its true intended use for XR from the FDA, and that Higgins shared that intent – is overwhelming, however. As President of the Spine Division, Higgins had spearheaded Synthes' effort to develop a radiopaque version of SRS for spine surgeons who used PMMA off-label in surgeries to treat VCFs. G.

Mem. 1, 2; see pp. 26-29, above. The VCF market was the market Synthes sought to capture with XR. G. Mem. 1. The documents and the testimony show that there was no other market of any significance for XR.

Higgins understood the choice Synthes had made in November 2001, and kept affirming later, to avoid the longer and more expensive IDE and PMA process, requiring clinical trials overseen by the FDA, in favor of the cheaper, faster 510(k) shortcut, in order to bring XR to market ahead of its competitors. Despite the concerns that the FDA expressed during the May 2002 conference call, about surgeons' use of bone void fillers in the spine for load-bearing indications, and the agency's request to Synthes for additional labeling for XR to specify that spinal load-bearing indications, such as vertebroplasty, were not included in the current indications for use, Synthes submitted the Special 510(k) without such language. G. Mem. 43. The FDA continued to insist on such language, however, until Synthes submitted the warning against VCF use that became part of the Norian XR label. The label of XR as cleared, bore the warning, "not intended for treatment of [VCFs]."

After the clearance, on January 16, 2003, Higgins, Huggins and Bohner all attended in-house meetings to approve a market introduction plan ("MIP") for Norian XR that discussed a supposed market for use of XR in the iliac crest, which is a part of the hip, when in fact no such market existed or plan was intended. Exhibit 3, MIP.[46] Higgins, Huggins and

[46] The forecast numbers in the MIP were accurate. That part of the MIP lists the SRS test market sites correctly, and states the correct forecast numbers for the use of XR in vertebroplasty and kyphoplasty surgeries. However, the market analysis section of the MIP, which names the iliac crest as the market for XR, was false, as confirmed by grand jury testimony of both the XR product manager and Scott Kramer, the Vice President of Spine Product Development. Kramer testified the market analysis portion of the XR MIP was "meaningless," and "a placeholder."

Bohner all signed the MIP that falsely identified the iliac crest as the market for XR. The fact that Higgins signed the false MIP adds to the other evidence showing that Higgins knew that the true intended use of XR was treatment of VCFs, and that he meant to hide that fact from the FDA. He went so far as to sign a false document, ensuring that if the FDA did come to investigate, there would be nothing to find concerning his development of XR for an unapproved and warned against use: the treatment of VCFs.

16. Paragraph 37 of the Presentence Reports

Paragraph 37 details how, on December 19, 2002, the FDA cleared Norian XR under Synthes Special 510(k) submission, with the same indication statement as SRS, and the warning bullet against VCF use, after Synthes management agreed to submit that warning to FDA for inclusion in the label. Defendant Huggins objects to this paragraph because it "fails to identify the fact that Mr. Huggins did not communicate with the FDA himself during the period at issue." Huggins Obj. p. 12. While the government agrees that on information and belief, Huggins did not personally communicate with the FDA when Synthes submitted the warning bullet for Norian XR, ¶ 37 does not say that he did, so this objection should be rejected.

17. Paragraph 38 of the Presentence Reports

Paragraph 38 describes the first death in the test markets. It states that, less than a month after the Norian XR clearance, on January 13, 2003, a surgeon who had participated in the SRS test market in the spine used SRS he had mixed with barium sulfate in a surgery using Synthes' cavity creation instruments to treat VCFs. That surgeon is identified in the Indictment as Doctor No. 4. A Synthes sales consultant was present during the surgery, and SRS was mixed with barium sulfate in the consultant's presence. The paragraph continues that after suffering a

hypotensive episode, Doctor No. 4's patient, an individual who suffered from numerous health conditions, including arterial sclerosis, coronary artery disease and previous myocardial infractions, died on the operating table ("the first death"). The paragraph concludes that, in conversations with three Synthes Spine employees, Doctor No. 4 did not rule out the mixed SRS as a cause of the first death.

Bohner objects to ¶ 38 on the ground that he "had no advance notice of this surgery or that a sales consultant would be present during this surgery. The consultant's presence during procedures involving off-label use of the. . . SRS product[] was against company instructions to the sales force in March 2001." Bohner Obj. p. 6.

Higgins objects to the statement in ¶¶ 38 and 39 "that Doctor No. 4 did not 'rule out' Norian SRS as a cause of death because it implies a connection between Norian and the death." According to Higgins, "Dr. No. 4 did not 'rule in' Norian SRS as a cause of death either." He continues that "[i]ndeed, not one of the doctors who used Norian on patients who died during surgeries could say that Norian was the cause of his patient's death." Higgins adds that he was not involved in the MDR process and cannot speak to the regulatory requirements of that process. Higgins Obj. p. 4.

As to Bohner's objection, ¶ 38 does not say that Bohner did have notice of this particular surgery or that a sales consultant would be present in the operating room. For that reason, his objection should be rejected. However, Bohner certainly knew about the SRS test market for the spine, in which this spine surgeon, Dr. Barton Sachs, had been trained. See, e.g., G. Mem. 33, Memorandum to Huggins, Higgins and Bohner on the SRS test market training dated June 4, 2002; G. Mem. 35, 36, meeting agenda for management meeting September 2002

and power point presentation on test market for SRS for the spine given at that meeting; G. Mem. 37, Safety Meeting materials listing Dr. Sachs as a test market site for Phase I, and see discussion at pp. 15-18 above and 75-78, below. As previously discussed, additional documents show that Bohner approved that test market as well. See G. Mem. 10, email exchange between Bohner and XR product manager dated May 22, 2002; G. Mem. 9, time line of meetings and approvals for SRS test market; G. Mem. 80, Bohner diary entry showing President's Meeting on May 22, 2002; G. Mem. 80, Bohner diary entry for May 27, 2004 during FDA inspection, noting that President's Meeting.

So while Bohner may not have had advance notice of the particular surgery that Dr. Sachs performed on January 13, 2003, it cannot have come as a surprise to him that such surgeries were occurring, especially since Dr. Sachs had been trained as part of the test market for SRS in the spine. Or that Spine sales consultants were present in the operating room despite the poorly-worded instructions about avoiding off-label promotion, sent by Huggins to the sales forces in March 2001 in response to the two Dr. Delamarter adverse events, G. Mem. 52 p. 2.

Higgins' objection is equally meritless. Paragraph 38 points out that Dr. Sachs did not rule out Norian SRS as a cause of his patient's death during surgery, because he said so in telephone conversations with three Spine Division employees afterwards.[47] Dr. Sachs and the three employees all confirmed this in their grand jury testimony. Dr. Sachs' conclusion on this point is significant because, by regulation, a device manufacturer must file an MDR with the FDA within thirty days, whenever the device manufacturer becomes aware of information from any source that reasonably suggests that the manufacturer's device might have caused or

[47] Their notes of those conversations with Dr. Sachs are G. Mem. 49, 50 and 51.

contributed to a death or serious injury. 21 C.F.R. § 803.10, 803-50. A medical device "caused or contributed to a death or serious injury" when the death or serious injury was, or may have been, attributed to the medical device, **or when the medical device was or may have been a factor in a death or serious injury.** (emphasis supplied). 21 C.F.R. § 083.3. So if the device cannot be ruled out as a factor in the death, an MDR must be filed.

The FDA makes MDRs available to doctors and other members of the public through searchable databases so that the public can be aware of serious risks associated with medical devices. 21 C.F.R. § 803.9. In addition, by submitting an MDR as required by law, a device manufacturer does not admit that the device has in fact caused or contributed to the death or serious injury being reported. 21 C.F.R. § 16. Finally, a medical device is also "misbranded" under the law if the manufacturer of the device fails or refuses to furnish to the FDA any material information concerning that device that is required to be reported on an MDR. 21 U.S.C. § 502(t)(2).

To say that Dr. Sachs did not "rule in" Norian SRS as a cause of his patient's death is true but meaningless, as is the fact that none of the three spine surgeons whose patients died during test market surgeries could conclude to a reasonable degree of medical certainty that Norian was the cause of their patients' demise. The point is that each of these patient deaths put the companies, and the individual defendants, increasingly on notice of the serious safety risks posed by using Norian in surgeries to treat VCFs.

18. Paragraph 39 of the Presentence Reports

This paragraph notes that even though Doctor No. 4 could not rule out SRS as a cause of the first death, the companies made the decision not to file an MDR on that death. It

points out further that, though not obligated to do so, neither company had an independent medical expert review the death.

Higgins objects that he was not involved in the MDR process and cannot speak to the regulatory requirements of that process. Higgins Obj. p. 4. But as defendant Bohner notes in his own objection to ¶ 39, when he (Bohner) first learned of the first, death, he "expressed concern that when a death occurs, a manufacturer only has a given number of days to report the incident to the FDA." Bohner Obj. p. 6. The evidence shows that Bohner expressed this concern at the MIP meeting on January 16, 2003, attended by all three defendants. Grand jury testimony shows that by January 16, 2003, defendant Higgins already knew about the first death, and at the meeting, defendant Bohner stated that there was only a five or seven-day window within which the manufacturer must report the death to the FDA on an MDR. According to one witness, at the MIP meeting Bohner was complaining that since Spine was sitting on this information, some time had already passed. Thus it appears that Higgins learned of the MDR process, at least in its broad outline, from Bohner at the MIP meeting.

Bohner's objection – that he expressed concern – goes to show that, in the MDR area as elsewhere, he knew what the law required. Yet the companies did not file an MDR on the first death. He goes on to say that Dr. Sachs' patient was elderly, with comorbidities, and to quote from company documents saying that Dr. Sachs did not believe that the product caused or contributed to the death. But according to the grand jury testimony and the notes of the three Synthes' employees who spoke with Dr. Sachs, he stated that while he did not specifically blame the material for the death, he was worried about using SRS again. The family of the patient refused an autopsy, so the cause of the first death cannot be ascertained. However, Dr. Sachs did

not rule out the SRS as the cause of the death, in the conference call or afterwards.

Bohner goes on to object that footnote 12 incorrectly implies that MDRs were not filed for any of the three patient deaths in the test market. This is not correct. Footnote 12 states that MDRs were filed for the second and third deaths, but not the first, Dr. Sachs' case, in which back-table-mixed SRS was used to treat VCFs.

Throughout his objection, Bohner claims that (1) Dr. Sachs reached a reasonable conclusion that Norian did not cause or contribute to the first death, and (2) based on that reasonable conclusion, the companies acted within the law in not filing an MDR on the first death. The regulations on which Bohner relies state that "manufacturers do not have to report adverse events for which there is information that would cause a person who is qualified to make a medical judgment. . .to reach a reasonable conclusion that a device did not cause or contribute to a death or serious injury." 21 C.F.R. § 803.20(c)(2). But as far as the first death is concerned, this argument is disingenuous at best. The complaint form generated when Dr. Sachs called Synthes to report the first death states that

> [d]octor was asked if the Norian product contributed to the death? Doctor's response, "If I thought there was a problem with the product I would not have used it."

From this exchange, the complaint taker concluded that Dr. Sachs did not attribute the product to the death. Exhibit 4, Complaint form, attached. But he had not even answered the question asked, much less reached a reasonable conclusion that the Norian did not cause or contribute to the death.

When a patient has died during surgery, and the company whose device was implanted has reliable information that the surgeon cannot rule out the device as a cause of the

death, it is astonishing that anyone would rely on a casual remark instead of investigating further. Despite his equivocation, the fact remains that Bohner, as the person to whom Regulatory employees reported, bore the ultimate responsibility for the decision not to file an MDR with the FDA concerning the first death; an MDR was required to be filed because based on the information available to Synthes, XR could not be ruled out as a cause of the death. Bohner failed in that duty.

19. Paragraph 40 of the Presentence Reports

This paragraph recounts how, in late January 2003, following the first death and eight months before Norian XR was released outside the test market, Bohner emailed Higgins, with a copy to Huggins, urging that management notify the Spine sales force that XR should not be promoted for off-label uses. In his email, Bohner argued that Higgins, as President of Spine, should send a proposed email about off-label promotion to the Spine sales force. In his email outlining the proposed communication to the Spine sales force, Bonner gave an example to clarify what off-label uses were forbidden: "[f]|or example, the FDA has required us to include the following warning in the product insert: 'not intended for treatment of vertebral compression fractures,'" showing that Bohner well understood the treatment of VCFs was forbidden. After Bohner sent his email to Higgins and Huggins, there was no communication that included both the language from the warning label for XR and an admonition that XR should not be promoted for off-label use that was sent to the Spine sales force. Higgins did forward the email to others in the Spine Division, including the XR product manager.

Bohner has several objections. First, the government agrees that in August 2003, Norian XR was released to the test market, so ¶ 40 should be amended to say that these events

occurred eight months before Norian XR was released *to* the test market, instead of *outside* the test market.

Bohner's second objection – that this paragraph fails to state that he forwarded his own email (containing both the language from the warning label for XR and an admonition that XR should not be promoted for off-label use) to an employee responsible for answering questions by sales consultants selling the Cavity Creation system (the instruments designed for vertebroplasty that were part of the Synthes System to treat VCFs) – is correct, but irrelevant. When Huggins never responded to Bohner's urging that management send an email to the Spine sales force calling attention to the warning on the XR label and notifying them that XR should not be promoted for VCF use, Bohner let the matter drop.

Bohner's third objection splits hairs. It is correct that off-label promotion of XR to treat VCFs violates the law, and ¶ 40 conveys that fact. The point is that, despite Bohner's clear admission of his awareness of what the XR label required – no promotion for treatment of VCFs – the sales force never received such a memorandum from anyone.

Bohner's fourth objection to ¶ 40 is telling. In the email he cites, Exhibit 5, attached, the Norian XR product manager is commenting on the binder that will go to the Spine sales consultants. She emails Bohner with a copy to Higgins, stating that sales consultants should be in the operating room when spine surgeons use XR off-label, because, "the product is technique sensitive. We need to have our sales consultants in the room to support its usage." Bohner writes back that:

> [w]e need to talk about this. I do not agree with much of what is said below! Unless we are very specific, we are going to have more problems. As far as not discouraging sales consultants from attending cases for off label usage, we already have an email from Mike

> Huggins in early 2001. Supporting off-label usage is a violation of federal law and an invitation for an instant warning letter. I do not support that type of activity. It puts the company and you in tremendous jeopardy. Did you know that?

Exhibit 5. Here is yet another clear admission of Bohner's awareness of what the XR label required – no promotion for treatment of VCFs, including not being in the operating room during surgeries to treat VCFs. But armed with that knowledge, knowing what his duty was, he failed to stop the illegal XR test market. And in December 2003, the memorandum from Bohner that went to the Spine sales consultant did not include both the language from the warning label for XR and an admonition that XR should not be promoted for off-label use.

20. Paragraph 41 of the Presentence Reports

This paragraph concerns how in late February 2003, the Synthes regulatory employee who had handled the XR 510(k) submission sent an email to the FDA, asking the FDA representative who had handled the clearance of XR whether, "as long as we clearly inform surgeons that Norian XR must be used with supplemental fixation (i.e., pedicle screws), we can indicate it [XR] for compression fractures in the spine?" Two days later, the FDA representative answered that Synthes could not. The email is G. Mem. 53. It is quoted in its entirety at fn. 7, p. 9 above.

Higgins states that he was "not involved" in the exchange with the FDA reflected in ¶ 41, and objects "[t]o the extent that the PSR suggests otherwise." Higgins Obj. p. 4. Bohner objects to the extent that ¶ 41 suggests that he either received it or knew about it. He explains that Vikki Hoffman did not report directly to him in February 2003, and concludes by noting that under the applicable regulations, an "informal email from an FDA representative does not constitute official FDA guidance." Bohner Obj. p. 8.

These objections should be rejected. Paragraph 41 does not state or suggest that Higgins was involved in the email exchange. Neither does it suggest that Bohner received this email or knew about it. However, the email does show that it was forwarded to defendant Walsh, later, on October 16, 2003. Bohner hired Walsh, and Hoffman had been Bohner's indirect report. Bohner's note that an email from an FDA representative does not constitute official FDA Guidance is correct, but irrelevant. The government does not argue that the defendants were legally bound to follow the views in the email. But with this email, as with other communications from the FDA, the agency gave Synthes (and later, Walsh) notice of its view of what the indication statement on the Norian XR label allowed. See United States v. Caputo, 517 F.3d 935, 941 (7th Cir. 2008). When they chose to go their own way later, they took a risk and could not then say that they did not know the FDA's views on what that label meant.

21. Paragraph 42 of the Presentence Reports

This paragraph describes the Safety Meeting on July 18, 2003, attended by defendants Huggins, Higgins and Bohner. That meeting is also discussed at pp. 15 to 18 above. Documents from the Safety Meeting include G. Mem. 37-42.

Higgins' sole objection concerning ¶ 42 is that he was "not interviewed or otherwise involved with the [2004] inspection." Higgins Obj. p. 4. Higgins is correct that unlike Huggins, Bohner and Walsh, he was not interviewed during the inspection. Thus fn. 13 of ¶ 42 of the PSRs should be corrected to reflect that fact. But contrary to Higgins' claim, he was "otherwise involved" in the inspection. Although he was not interviewed while the FDA inspected the Norian facility in West Chester, leading the FDA to find that Norian had failed to submit an IDE before carrying out the test market of Norian XR (i.e., that Norian had conducted

an unauthorized clinical trial of Norian XR through the so-called test market), Higgins participated in at least one meeting afterwards at which the participants wrestled with how to respond to the finding, and out of which came a false response authored by Walsh. Exhibit 1.

Bohner makes two objections. He objects to ¶ 42 insofar as it "suggests that he believed at the time of this meeting that proceeding with the test market plan was illegal." Bohner Obj. p. 8. This raises a factual issue that the Court must resolve at sentencing. The government's response is the same as that concerning ¶ 20, above (see pp. 12-13, and response pp. 14-22).

In his other objection, Bohner repeats his arguments that Synthes did not file an MDR on the first death relying on Dr. Sachs' conclusion, and that, according to the XR product manager, the pilot studies were not to be used in making conclusions in human clinical experience." Bohner Obj. p. 8. In downplaying the alarming news about Norian that was discussed at this meeting, Bohner is clutching at straws.

The issue at the Safety Meeting was whether XR was safe enough to bring to market. The minutes show that the pilot studies were discussed, and that follow-up studies proposed by Dr. Chapman had not yet been begun. The participants, including Bohner, were concerned over the abstract that Drs. Mirza and Chapman had written of the article they wanted to be published by ORS (Orthopaedic Research Society); the minutes state, "[p]otential to start on the defensive based on the language in the abstract." G. Mem. 37. This refers to the finding that Norian cements appeared to cause blood clots. See also G. Mem. 80, fn. 13, p. 17 above (Bohner diary entry for Safety Meeting). More generally, the participants discussed whether Synthes should start a second phase of the Test Market, or whether instead Synthes should seek

an IDE in order to conduct clinical trials of Norian XR, so that it could be cleared for treatment of VCFs.

Bohner was the most senior Regulatory person attending the Safety Meeting. At that time, Bohner knew that test markets could not be for off-label uses, but that this meeting had been called to approve the continuation of a test market for the off-label use of treating VCFs. In addition, Bohner knew that the test market would be collecting data concerning the off-label surgeries, without having the FDA's permission via an IDE. At this meeting, as mentioned above, the decision was made to continue the test market regardless.

Huggins objects to ¶ 42 for incorrectly stating that all 34 of the Phase I test market surgeries were to treat VCFs. Eight were to treat VCFs and 26 were for burst fractures, he claims. Huggins Obj. p. 10. Huggins is correct but all 34 were illegal nonetheless, for all 34 resulted from Synthes' Spine employees training the Spine surgeons to mix SRS with barium sulfate in contravention of the SRS label, and Huggins knew this. See pp. 33-40, above.

The remainder of Huggins' objections to ¶ 42 lack merit. As proof of his allegedly good intentions, Huggins explains that he invited Dr. Helfet, a trauma surgeon and Synthes board member, to attend the Safety Meeting, which he did, by telephone. Unfortunately, however, Dr. Helfet was misinformed about the Norian XR label; apparently no one from Synthes showed him the label with its warning bullet.[48] Huggins argues that "the point of the meeting was not to address product risks that were believed to be outside the scope of the label,

[48] Dr. Helfet testified in grand jury that in July 2003, he believed that XR was approved for use in treatment of VCFs, and that no one at Synthes had shown him the XR label with its warning bullet. Helfet testified that he thought there was no FDA impediment to marketing XR. Helfet testified that he also thought that Synthes should do a clinical study with 200-300 patients. Helfet explained that because he thought that using XR to treat VCFs was on-label, he did not think an IDE was necessary.

but to go beyond, as a matter of good corporate governance, what was legally required." On the contrary, the point of the meeting was to decide whether it was safe to bring XR to market. And what the law required was clear: that this significant risk device not be tested on humans without the FDA's approval. The law's requirements were especially urgent here in light of the significant risks to patient safety.

On the eve of Phase II of the test market to introduce XR for VCFs, Huggins convened the Safety Meeting. As described above, the participants at the Safety Meeting discussed the first death, the poor pilot study results and the other two, non-fatal VCF adverse events, but decided to go ahead with Phase II of the XR test market anyway.

22. Paragraph 43 of the Presentence Reports

This paragraph describes an August 14, 2003 strategic planning meeting on Norian XR attended by Huggins, Higgins and Bohner,[49] other employees, and a number of surgeons, including Doctor No. 3. At that meeting, the issue of an approved clinical study of XR was raised again. Doctor No. 3 reported that XR "is the safest material to use, especially with a low pressure system." Huggins noted that Synthes had a "poor record of PMA approvals," and Huggins and Higgins directed that the XR "test market" would continue, despite a presentation made at the meeting on vertebroplasty and XR and a recommendation by one of the doctors that an FDA study of XR be conducted to gain approval for vertebroplasty.

The government notes that it was Doctor No. 3 (Jens Chapman), one of the University of Washington researchers, who recommended that Synthes undertake an FDA study

[49] As Scott Kramer's minutes of the Strategic Planning Meeting show Bohner as attending, and Bohner's diary entry for August 14, 2003 supports this ("IDE for vertebroplasty"), ¶ 43 should be amended to reflect that Bohner attended this meeting.

of XR to gain approval for vertebroplasty. This meeting is discussed above at p. 19.

Only Huggins objects to ¶ 43, claiming that meeting participants were "discussing ways to alleviate risk and improve outcomes above the floor set by the law"; that he "attempted to do the right thing when presented with issues relating to Norian"; and that he "was not involved in a sinister discussion as the PSR implies." Huggins Obj. p. 10-11. The government agrees that, as shown by the meeting minutes, Huggins knew the right thing to do. But he did not do it. Instead, when Dr. Chapman urged an FDA study of Norian XR to gain approval for vertebroplasty, Huggins argued that Synthes had a "poor record of PMA approvals" – and directed that the Norian XR test market would continue.

The Synthes-produced documents show that Walsh – who before coming to Synthes graduated from law school (1994) and worked in regulatory affairs in the device industry for almost a decade – became a part-time Synthes employee on June 15, 2003. Because he held himself out as a lawyer, Walsh's opinions on regulatory matters at Synthes carried significant weight. Walsh began by reporting to defendant Bohner (whose diary refers to frequent calls and meetings with Walsh throughout mid-2003), in the position of Synthes Spine Director, Spine Regulatory and Clinical Affairs, with responsibility for overseeing the Spine Clinical/Regulatory department, including hiring. On August 15, 2003, the day of the first Norian XR test market training session and a few days before his start date as a full-time employee, Walsh was sent the minutes of the August 14, 2003 strategic planning meeting that is discussed in ¶ 43. Exhibits 6, 7, attached. As set forth in those minutes, participants discussed the Norian XR indications, the test market, and Dr. Chapman's recommendation that an FDA study of Norian XR be conducted to gain approval for vertebroplasty. So by August 15, 2003, defendant Walsh was apprised of the

test market.

23. Paragraph 44 of the Presentence Reports

This paragraph discusses the first surgeon training meeting of the Norian XR test market, held on August 15 and 16, 2003 in San Diego, California. This training is discussed in detail at pp. 19-20, above.

Defendant Bohner claims that he had little or nothing to do with the surgeon training, Walsh pleads ignorance, while Higgins argues that it was all perfectly legal. Bohner objects that he "did not attend a test market training session. He did not supervise the employees who organized and conducted the test market. We are not aware of any evidence that [he] reviewed or approved the test market presentation or the evaluation form at the time that the test market was occurring." Bohner Obj. p. 9. Walsh offers that he did not approve the test market either, claiming that "the first two surgeon forums were planned and approved prior to [his] employment with Synthes, and he neither reviewed nor approved the presentation materials used at the forums or in other 'test market' activities.'" Walsh Obj. p. 2. Higgins renews the objection he made to ¶ 28, concerning the test market for SRS in the spine. He adds that the surgeon trainee materials included a copy of the Norian XR label, including the warning bullet. Higgins Obj. pp. 4-5. All of these objections are meritless and ¶ 44 should remain as is, as explained below.

The government refers the Court to pp. 14-22 above, for its response to Higgins' broader argument that the XR test market was legal. Suffice it to say that it was not. If possible, it was even more blatantly illegal than its predecessor, the SRS test market. By August 2003, based on the first death, the risks posed by Norian were even clearer than they had been before;

the company had promised the FDA that it would not promote XR for VCF use without the proper regulatory authority; and the label warned against VCF use. Higgins knew all these things, yet pushed ahead with the surgeon training. Higgins' narrower objection, that the surgeon trainee materials included a copy of the Norian XR label, including the warning bullet, proves nothing. The company could not escape liability for training surgeons how to use Norian XR in surgeries to treat VCFs – the prohibited indication – by including a slip of paper containing the label into training materials, and Higgins knew this.

While Bohner may not have attended test market training sessions, or supervised the employees who organized and conducted the test market, or reviewed or approved the test market presentation or the evaluation form at the time that the test market was occurring, that is not a valid objection to ¶ 44. He was well aware of the test market, having approved its first phase, Phase I, with SRS; having attended the Safety Meeting; and having attended the strategic planning meeting August 14, 2003.

As mentioned above in connection with ¶ 43, by August 15, 2003, Walsh was apprised of the test market, from the strategic meeting minutes.

24. <u>Paragraph 45 of the Presentence Reports</u>

This paragraph recounts events on September 19, 2003, concerning the death of Doctor No. 5's patient during a surgery using cavity creation instruments to treat VCFs. The patient died on the operating table after suffering a hypotensive episode ("the second death"). Doctor No. 5 noted a cement leak, and believed that it was the cause of the episode, and could not rule out XR as a cause of the second death. Synthes and Norian filed an MDR on the second death that was vague as to the surgery and its details. Again, neither company had an independent

medical expert analyze the death.

Bohner objects to ¶ 45 because he "had no advance notice of this surgery or that a sales consultant would be present during this surgery." He argues further that the MDR was not vague because it stated that a patient had died during use of Norian XR in a spinal procedure, and that the "[s]urgeon complained that a patient expired during a three level vertebral body augmentation using Synthes Cavity Creation and Norian XR-010 Bone Void Filler." Bohner Obj. p. 9.

As to Bohner's objection, ¶ 45 does not say that Bohner did have notice of this particular surgery or that a sales consultant would be present in the operating room. For that reason, his objection should be rejected. However, Bohner certainly knew about the XR test market, in which Dr. Hieu Ball, the partner of this spine surgeon, Dr. Nottingham, had been trained, based on Bohner's presence at the Safety Meeting and the strategic planning meeting, above, as well as his close involvement in the first phase of the XR test market, that is, the test market for SRS in the spine. And as stated above, this MDR (as well as the MDR on the third death) were brief, vague and did not mention the terms "vertebroplasty," "kyphoplasty," or "vertebral compression fracture" in order to conceal from the FDA and spine surgeons the fact that the second (and third) deaths had occurred during surgeries to treat VCFs, in which cement leakage had been noted. Thus Bohner's objection to the term "vague" in ¶ 45 should be rejected.

Walsh begins his Specific Objection II.A (p. 2) with the factual fallacy that he "does not have a basis to admit or deny the accuracy" of ¶¶ 45 to 46 (dealing with the second death on September 19, 2003 and related events). But in fact he attended a high-level company meeting on September 23, 2003 that analyzed the death, the risks of continuing with the test

market, and the "[n]eed to assemble the data . . . [and] look at trends," including comparing the incidence of two deaths in few Norian XR surgeries with adverse events in vertebroplasty and kyphoplasty surgeries in which non-Synthes acrylic bone cement (PMMA) was used. See Exhibits 8 and 9, attached. Based on discussions at that meeting, Walsh researched and reported to the Norian XR product manager, and later to defendant Bohner (who in turn forwarded the information to defendants Huggins and Higgins) publicly available adverse event information on bone void fillers and acrylic cements. Exhibits 10 and 11, attached.

25. Paragraph 46 of the Presentence Reports

This paragraph describes how, despite the second death, the companies continued the second surgeon training meeting of the XR test market on September 19 and 20, 2003, in Charlotte, North Carolina. This training is discussed in at p. 21 above.

While Walsh objects to ¶ 46, claiming that he "does not have a basis to admit or deny the accuracy" it, this is not accurate. As stated above, based on Walsh's attendance at the September 23, 2003 management meeting that analyzed the second death, the risks of continuing with the test market, and the "[n]eed to assemble the data . . . [and] look at trends," including comparing the incidence of two deaths in few Norian XR surgeries with adverse events in vertebroplasty and kyphoplasty surgeries in which non-Synthes acrylic bone cement (PMMA) was used, Walsh was aware of the XR test market.

26. Paragraph 47 of the Presentence Reports

This paragraph recounts how, days after the second death, a spine surgeon identified in the Indictment as Doctor No. 6 (Dr. Joe Lane) told Synthes of a number of concerns he had about XR and the test market. He stated that he believed that XR was "potentially

dewatering and causing episodes of hypotension." He also stated that, because the Norian XR "test market" was collecting information from surgeons performing surgeries to treat VCFs, he believed that Synthes was required to go to each institutional review board ("IRB") of each hospital participating in the "test market" Doctor No. 6 also told Synthes that, in light of the company's "test market" activities, the company should goto the FDA immediately to negotiate the removal of the warning on theXR label, "not intended for treatment of vertebral compression fractures." Doctor No. 6 also told Synthes that, in his view, Synthes had risk management problems and needed more over sight of its clinical and compliance issues. Huggins was informed of Doctor No. 6's views. Huggins was also the most senior manager present at meetings following the death of Doctor No. 5's patient. The outcome of those meetings was that, despite the new death and further results from the University of Washington of the same tenor, the studies on humans with Norian XR in the test market would continue.

The government requests that ¶ 47 of the PSRs be amended to reflect that all four defendants, not just Huggins, learned of Doctor No. 6's comments by October 1, 2003. G. Mem. 68.

In Specific Objection II.A (p. 2), Walsh denies contemporaneous knowledge about PSR Paragraph 47 (concerning Doctor No. 6's September 26, 2003 stated concerns about Norian XR and its test market).[50] But e-mails detailing those concerns was forwarded to Walsh on October 1, 2003. G. Mem. 68; Exhibit 15, attached. Indeed Walsh, who was evaluated during this period for his ability to "[e]stablish[]/build[] infrastructure for a Clinical/Regulatory

[50] Walsh claims that his "sole involvement relating to the events described in this Paragraph was to conduct research on adverse events involving [PMMA] at the request of the Norian XR product manager following these events." Walsh Obj. 2.

department" Exhibit 16, attached, was the Synthes employee who, by virtue of his position, was perforce concerned with Doctor No. 6's comments. (These included statements that Synthes, as evidenced in the conduct of its Norian XR test market, lacked necessary in-house regulatory capabilities, and that discrepancies between the test market and the Norian XR label needed to be addressed.) In a follow-up email the following day, defendant Bohner reminded Walsh that Doctor No. 6's proposal was consistent with an earlier, internal company proposal. Exhibit 17, attached. Once again, Walsh's claimed lack of knowledge is belied by the documents.

27. Paragraph 48 of the Presentence Reports

This paragraph describes the internal IDE proposal that was circulated within Synthes to all four defendants. It is described and quoted at length in the Indictment, ¶ 76. The proposal is G. Mem. 71.

Both Higgins and Bohner object to ¶ 48's statement that they did not share this internal IDE proposal with the FDA, insisting that there is no requirement that a company share its draft IDE proposals with the FDA, which of course there is not. This objection should be rejected.

Bohner objects further to ¶ 48 because, he argues, the quoted portion of the internal IDE proposal does not concede that the companies were engaging in off-label promotion of XR. Perhaps the quoted portion does not, by itself, but when read as a whole, the proposal concedes that much and more, making it easy to see why the defendants did not share this IDE proposal with the FDA, and why their emails expressed such concern about the product manager's circulating it in the first place.

After discussing the Norian XR test market and the fact that two deaths had

occurred as part of the test market, the IDE proposal goes on to discuss competitive activity with other products, all of which were for vertebroplasty and kyphoplasty surgeries to treat VCFs, stating that XR was the only product that the FDA had required to add the warning bullet, and stating that "[f]rom a competitive standpoint, Norian XR is at a significant disadvantage. All of *our competitors* are using this bullet as a selling point against Norian XR. Rightly so, many surgeons are listening." Indictment ¶ 76 (emphasis supplied); G. Mem. 71. In the context of a proposal to seek FDA permission to conduct clinical tests on XR in surgeries to treat VCFs, these words were damning indeed. A clearer admission that the companies had been promoting XR in the VCF market would be hard to write. But all four defendants saw this document when it was circulated, and none denied the facts stated in it.

In his Specific Objection II.C (pp. 4-5), Walsh objects to ¶ 48, but the basis for his objection is difficult to discern. His objection to ¶ 48 is of a piece with his various other specific objections, where he suggests that he "was not aware of the substance" of the Norian surgeon training forums (Specific Object II.A, at 2), "was not aware that Synthes was, in fact, promoting Norian XR off-label for [treatment of VCFs]" (Specific Objection II.C, at 5), and "was not aware that surgeons had been trained relating to the use of Norian XR to treat VCFs" (Objection II.E, at 8). All of these claims are contradicted not only by the documents already mentioned but also by notes from the Synthes Halloween 2003 management meeting as well as other November 2003 company documents.

On October 31, 2003, Walsh was the highest-ranking regulatory employee at a high-level meeting regarding Norian XR that included defendants Huggins and Higgins. Notes from the meeting state, regarding Walsh and the follow-up to the second death: "John: IDE --

reasons -- competitive status -- what studies have been done? MDR [Medical Device Report] filed? Who to file? Why not satisfactory? Slow down training -- advised IDE[.]" The notes further refer to discussion about the University of Washington preclinical study results. Exhibit 18, attached.

On November 10, 2003, the Norian XR product manager e-mailed Walsh and others in "follow-up to last week's meeting" by attaching a "proposal for pursuing the vertebral compression fracture indication for Norian XR," which "[a]s we discussed, John Walsh will begin" to discuss "with the FDA."[51] The attachments to this e-mail include descriptions of: (a) the Norian XR test market; (b) the *first and second* patient deaths; and (c) further proposed University of Washington safety studies. (E.g., "Synthes is closely monitoring the limited release phase. An evaluation form has been collected for every case completed to date. Thus far, ~ 100 cases have been done using Norian XR in a variety of surgical applications. These . . . include treatment of osteoporotic VCFs. . . . During the limited release two questionable outcomes were encountered [which are described in detail later in the document], resulting in two patient deaths. . . . The [future] forum presentations will be 100% delivered by . . . surgeons."). G. Mem. 71; Exhibits 19 and 20, attached.

In addition, on December 16, 2003, Walsh signed for Synthes Regulatory Affairs the "Approval for Release to Sale form for Norian XR. Exhibit 22, attached. This authorized release of XR to accounts with surgeons who had participated in the test market and who were

[51] In his Specific Objection II.C (pp. 4-5), Walsh goes to much length to appear to dispute ¶ 48 regarding the initial November 2003 IDE proposal but, stripped bare, his objection is an acknowledgment of facts that he cannot deny -- that he saw the November 2003 document when it was circulated and that the document says what ¶ 48 says that it says. See G. Mem. 70, 71.

trained at a test market forum. Exhibit 23, attached.

28. Paragraph 49 of the Presentence Reports

This paragraph describes how, at the end of December 2003, defendant Walsh approved the XR Technique Guide for release to the Spine sales force, despite the fact that the Technique Guide did not disclose or otherwise state the specific warning on XR's label, "not intended for treatment of [VCFs]," and not withstanding the fact that the Technique Guide contained x-rays of VCFs, some of which were x-rays of the spine of Doctor No. 4's patient who had died on the operating table in January 2003 during a surgery to treat VCFs. This paragraph also notes that at the end of December 2003, Synthes released XR for sale beyond the original "test market."

Higgins refers to his objection to ¶ 28 and argues that a test market is not inherently improper. Again, this raises a factual issue to be resolved at sentencing, as the XR test market was illegal and Higgins knew it, as discussed above.

Bohner objects that ¶ 49 should say that at the end of December 2003, Synthes made Norian XR "available for sale on a limited basis," only to the spine surgeons who had participated in the test market and those who would be trained at one of the upcoming surgeon fora. Bohner Obj. p. 10. While Bohner is correct that Synthes made this announcement, the December 2003 release did make XR available beyond the initial test market: additional surgeon training was planned, in the form of surgeon fora (one surgeon forum did take place, in January 2004, see ¶ 50, below, and a second surgeon forum was cancelled due to the third death). so the objection should be rejected. Bohner "objects" further that he did not review or approve the Technique Guide, Walsh did, and that he is unaware of any evidence that he was consulted by

Walsh. But ¶ 49 does not say that Bohner was involved in this review or approval, it states that his direct report, Walsh, whom he hired was, so this objection should be rejected as well.

In his Specific Objection II.D (pp. 6-8), Walsh says much to create the appearance that he is disputing ¶ 49, but beneath that veneer is his concession that in December 2003 he approved the Norian XR Technique Guide, which lacked the product's warning bullet and which contained VCF x-rays.[52] He cannot credibly refute that he was responsible for reviewing carefully the Technique Guide for regulatory compliance and for inquiring about any regulatory problems, and it is of no significance that he did not prepare the Technique Guide but only reviewed it. It is indisputable that had he rejected the Guide, it would not have been released to the sales force. As he notes in his Objections (p. 7), he was not merely a regulatory supervisor, but also the holder of a law degree, and Synthes employees paid him deference. At the January 10, 2004 Norian XR surgeon forum in Dallas, before the third death, Synthes distributed the Technique Guide and CD-ROM not merely to Synthes sales representatives but also to surgeon attendees. See Exhibit 24, attached.

Walsh is disingenuous in arguing on pages 7-8 of his objections that he is essentially saved by his reliance on his own legal advice that the Technique Guide and CD-ROM, notwithstanding their inclusion of information/photographs on the off-label use of Norian XR for treatment of VCFs, were First Amendment-protected, non-promotional, educational/scientific speech under the reasoning in Washington Legal Foundation v. Henney, 202 F.3d 331 (D.C. Cir. 2000), and Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51 (D.C. Cir. 1998). As a

[52] He omits mention of his sign off on a "Final Review, Revision 2," for the Technique Guide, with checking of a box for "Submit another layout/proof," on November 18, 2003. Exhibit 25, attached.

lawyer and regulatory specialist, Walsh knew that the FDA considered such materials to be promotional "labeling" that had to be consistent with FDA's clearance of Norian XR.[53] He further knew that the First Amendment does not protect commercial speech that is misleading. Plainly, the Technique Guide, which was distributed to surgeons at the January 2004 surgeon forum, by eliding the Norian XR warning bullet, and by including photographs of Norian XR VCF surgeries, was non-First-Amendment-protected, misleading promotional material about the regulatory status of Norian XR.

29. Paragraph 50 of the Presentence Reports

This paragraph recounts how, on January 10 and 11, 2004, the companies held the first surgeon forum, at which approximately 30 surgeons were trained to use XR to treat VCFs, and at which the companies delegated to Doctor No. 4 the task of explaining the warning on XR's label, "not intended for treatment of [VCFs]." Doctor No. 4 re-worded the warning, which led to questions from the surgeons in attendance. Company representatives did nothing to dispel any confusion that Doctor No. 4's presentation may have caused. The paragraph also notes that the XR Technique Guide went to all attendees, including the 30 surgeons.

Higgins and Bohner object that they did not attend the surgeon forum. Higgins Obj. p. 5; Bohner Obj. p. 10. As to Higgins, this is immaterial, as he (and Huggins) approved this forum, according to what the FDA investigator was told during the inspection, and as

[53] The term "labeling" encompasses the label accompanying the device, as well as all other written, printed, or graphic material "(1) upon [the device] or any of its containers or wrappers, or (2) **accompanying such [device**]." 21 U.S.C. § 321(m) (bold added); Kordel v. United States, 335 U.S. 345, 350 (1948); United States v. Urbuteit, 335 U.S. 355, 357 (1948) (both holding that material that explains the use of an article regulated under the Act - such as a device - for a particular indication is labeling whether or not the material is physically attached to or shipped at the same time as the article).

corroborated by Bohner's entries in his diary for May 24 and 25, 2004: "Dallas Weekend Forum Approval – MH, LH, TH, SK." For the next day, May 25, 2004, Bohner wrote: "Despin requesting titles and office locations for MH, TH, LH and SK – approved Dallas Surgeon training forum." G. Mem. 80, p. 024541, 43. For his part, Bohner does not state that he was unaware of the surgeon training forum at the time. Both objections should be rejected.

30. Paragraph 51 of the Presentence Reports

This paragraph describes the third death in the test markets. On January 22, 2004, a spine surgeon identified in the indictment as Doctor No. 7 (who at the time was partners with Doctor No. 6) used Norian XR in a kyphoplasty surgery to treat VCFs. A hypotensive event occurred, consistent with pulmonary embolism, and the patient died on the operating table. Doctor No. 7 could not rule out Norian XR as a cause of the third death. Once again, a Synthes sales consultant was present in the operating room during the surgery that resulted in the third death. Although the companies filed an MDR on the third death, that MDR was vague as to the surgery and its details. Moreover, Synthes and Norian failed to supplement that MDR when Synthes received an autopsy report, even though the autopsy report contained new information that Synthes had not put in the original MDR, that is, that the patient had a history of osteoporosis and a vertebral compression fracture, for which a kyphoplasty surgery had been performed, and that at autopsy, foreign material was found in the L2 vertebral body and in microscopic vessels of the lungs.

In his Specific Objection II.A. (p. 2), Walsh contends that he "does not have a basis to admit or deny the accuracy of" PSR ¶¶ 50 and 51 (concerning the January 2004 surgeon forum in Dallas and the third death, including how the death was reported to the FDA). But at

least as to the third death, this is untrue. Walsh attended the meetings (also attended by defendants Higgins, Huggins, and Bohner) held on January 23, 2004 and January 27, 2004 to discuss the third death and its implications for the Norian XR test market. He attended a similar, follow-up meeting in early February 2004. In February and March 2004, he also exchanged e-mails with a Vice President of Clinical Research and Regulatory Affairs for a competitor company, Kyphon, who by February 5, 2004 had heard about the third death and asked for details and a copy of the autopsy report. In early March 2004, Walsh e-mailed the Kyphon V.P. that he had met with the surgeon partner of the third death surgeon to discuss the third death. Exhibit 26, attached. Walsh received a copy of the autopsy report for the third death on March 24, 2004, Exhibit 27, which shortly thereafter he characterized to the Kyphon V.P. as concluding "nothing alarming regarding either Kyhon's or Synthes' products." Exhibit 26, attached.

Higgins objects to ¶ 51 because it does not mention that the patient who died was 83 years old with many other health problems. This objection speaks volumes about Higgins' history, characteristics and his prospects for the future.

As Higgins well knows, the target patient population for surgeries to treat VCFs is elderly. Such persons commonly have other health problems. Synthes, through Higgins and the other individual defendants, knew this when they set out to capture the VCF market. See, e.g., G. Mem. 1, 19. To suggest that defendants' crime is somehow mitigated by the fact that the subjects of their unauthorized human experimentation had a diminished life expectancy is morally repugnant as well as legally irrelevant. This Court need not determine whether the government has shown to a reasonable degree of medical certainty that Norian caused the three reported patient deaths and other associated adverse events. Rather, the Court must determine

the individual defendants' knowledge and intent, and the likelihood that they will commit crimes in the future. The fact that the patients who died during the test market surgeries were old and frail, as was to be expected, is simply not relevant to that determination.

31. Paragraph 52 of the Presentence Reports

This paragraph summarizes events after the third death. The companies did not recall XR from the market. A recall would have forced the companies to inform the FDA of the details of all three deaths. Instead, Synthes and Norian left XR on the market, and sent surgeons a misleading "dear surgeon" letter, signed by Huggins in his capacity as President of Synthes North America. The "dear surgeon" letter admitted that use of XR to treat VCFs was off-label but explained that such use was off-label because it was "intrinsic to the stability of the bony structure." The letter was silent about the warning bullet and further omitted to state that (1) Synthes had conducted a "test market" in which it had trained surgeons to use XR to treat VCFs; (2) the pilot studies indicated that Norian appeared to be a thrombogenic agent;[54] and (3) three patients had died on the operating table when spine surgeons had used Norian XR or its predecessor, SRS, off-label to treat VCFs.

Because Walsh was the primary author of the "Dear Surgeon" letter, it is unsurprising that he attacks ¶ 52's description of the letter.[55] According to Synthes' privilege log in this matter, just days after the third death Walsh wrote an e-mail to Synthes counsel seeking advice on draft "Dear Doctor" letters regarding Norian XR. On January 28, 2004, the Norian XR

[54] A thrombogenic agent is one that causes blood clots.

[55] The draft Dear Surgeon and Dear Consultant letters that he sent to outside counsel and to defendants Higgins, Huggins, and Bohner for review on February 5, 2004 are identical to the letters that were later sent to surgeons and counsel on February 16, 2004. See Exhibits 31 and 32, attached.

product manager wrote to Walsh proposing that e-mails be sent to surgeons immediately advising them that: (a) there had been a "complication" in the test market "while using Norian XR"; (b) "this incident has given the company pause regarding the use of calcium phosphates in these types of procedures"; and (c) "as a cautionary measure, Synthes is stopping the distribution and usage of Norian XR until were are 100% sure that Synthes and the surgeons we work with fully understand the chemical and physiological interactions of calcium phosphate cements as they apply to the spine." Exhibit 30, attached. But no such letter was ever sent. Rather, the Walsh-drafted "Dear Surgeon" letter that was sent to test market surgeons weeks later, on February 16, 2004, made no such reference to a test market adverse event, to concerns about calcium phosphate products as contrasted with acrylic cements, or about stopping usage of Norian XR while safety concerns were addressed.

Finally, Walsh's semantic acrobatics regarding the proper meanings of the terms "vertebroplasty" and "VCFs" are hollow, irrelevant apologetics. Of course, technically, vertebroplasty is a procedure and a VCF is a medical condition, but at Synthes and within the industry vertebroplasty has been loosely used to refer not just to percutaneous surgical procedures to treat VCFs but also to VCFs. In fact, in his November 11, 2003 email, Walsh himself used the term "vertebroplasty" when referring to VCFs. ("I have not heard back from the agency regarding our interest in pursuing an IDE for vertebroplasty."). Exhibit 33, attached. And he received emails in which the Norian XR product manager and others did the same. And while Walsh insists that he believed treatment of burst fractures to be within the label, this is more of the same. From the "Dear Surgeon" letter that he authored, it is clear that Walsh well understood the indications statement in the Norian XR label: that indications statement alone, without

reference to the warning, excluded treatment of VCFs as weight-bearing. In light of that indication statement, for him to claim that burst fractures[56] were within the label is akin to a speeder saying that he knew he could not go 45 miles an hour, but he believed in good faith that he could go 80. Neither did any of the other defendants believe that treatment of burst fractures was within the XR label, for if they had, they would have used the treatment of burst fractures as the safe "place holder" they needed in the Norian XR MIP, instead of the non-existent market for use in the iliac crest.

Defendant Higgins objects to ¶ 52 on the ground that by the time the "Dear Surgeon" letter went out, he was no longer President of the Spine Division, "and was not involved in the dissemination of the letter." Higgins Obj. p. 5. But as stated above in the government's response to Walsh's objections to ¶¶ 50 and 51, meetings were held in the wake of the third death, and Higgins attended those meetings. Like Huggins and Bohner, he received a draft of the Walsh-drafted "Dear Surgeon" letter before it was sent out. Exhibit 31, attached. He continued to be involved, although less centrally. Higgins' objection to ¶ 52 should be rejected.

Defendant Huggins asserts that it was a matter of "corporate governance" – and not an admission that he had done anything wrong– to issue the "Dear Surgeon" letter admonishing doctors to not perform off-label procedures with Norian XR (or any other bone cement) rather than institute a product recall after a patient died during an operation involving Norian XR in January 2004. Huggins then complains that ¶ 52 does not mention that "no legal

[56] Whereas a VCF involves the front half to two-thirds of the vertebral body, a burst fracture also involves the back cortex as well.

requirement for a recall existed." Huggins Obj. p. 11. Bohner's objection to ¶ 52 is to the same effect. Bohner Obj. p. 11. These objections are misleading at best.

For the vast majority of products regulated by the FDA, there is no "legal requirement" for manufacturers to recall products that violate the FDCA. Product recalls – which include physically removing the product from the market as well as corrections to the product in place – are generally voluntary actions "that take place because manufacturers and distributors carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise defective." 21 C.F.R. § 7.41(a). While manufacturers of other FDA-regulated products are *requested* to report removals and corrections undertaken to remedy a violation of the FDCA, device manufacturers are legally *required* to report voluntary removals and corrections undertaken to reduce a health risk posed by the device, or to remedy a violation of the FDCA that may present a risk to health. 21 U.S.C. § 360i(g)(1)(A),(B).

The FDA also has the authority to "legally require" a medical device recall if there is sufficient evidence for the Secretary of Health and Human Services to find that there is "reasonable probability that a device intended for human use would cause serious, adverse health consequences or death" and after the manufacturer is afforded an opportunity for an informal hearing. 21 U.S.C. § 360h(e)(1). A recall under this authority, however, depends on manufacturers fulfilling their other duties under the FDCA to provide information to the FDA, mainly through adverse event reporting, 21 U.S.C. § 360i, and by properly reporting voluntary product removals and corrections. 21 U.S.C. § 360i(g)(1).

In this case, Huggins' argument that there was no legal requirement to recall the Norian XR at the time of the "Dear Surgeon" letter is misleading at best. The FDA did not have the information to demand a recall because Synthes either did not provide it, or provided it in a way that it was difficult to attribute to the device or to the use in surgeries to treat VCFs. Huggins, Bohner and Synthes also did not report to the FDA that they issued the "Dear Surgeon" letter directing that doctors not use Norian XR off-label. While this reporting may not have been "legally required" since the surgeon notification did not fit into the technical definition of a "correction" since it was not relabeling the product but was merely directing surgeons to follow the labeling, it exemplifies that the company was run with an eye towards avoiding reporting and regulation rather than protecting the public health.[57]

32. Paragraph 54 of the Presentence Reports

This paragraph concerns the obstruction of justice enhancement and notes that while the presentence writer did not apply the upward adjustment under § 3C1.1, the Court may consider any relevant conduct, including the allegedly false statements made during the May-June 2004 FDA inspection by defendants Huggins, Bohner and Walsh, under U.S.S.G. §§ 1B1.3 and 1B1.4. Those statements are set out in Counts Five, Six, Seven and Eight of the Indictment.

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[57] Defendant Huggins also claims that the PSR fails to put the offense conduct in perspective because it does not reflect that since 2004, FDA "specifically has cleared three bone cements for the treatment of VCFs in the spine." Huggins Obj. p. 15. The three clearances that Huggins references – k003801, k050864, and k080108 – are all for *acrylic* bone cements and only highlight Huggins' criminal conduct rather than mitigate it. Synthes and Huggins planned to market their re-absorbable calcium phosphate cement as an alternative to (and as superior to) the synthetic competitors. The clearances for these synthetic products for the specific indication of treating vertebral compression fractures during and after Synthes' illegal test market, corroborate the race to market between the two competing products, as well as exemplify that there is a correct way to come to market, i.e., by specifically seeking and attaining FDA clearance rather than by lying to FDA about the true intended use of the product.

All three defendants object to this statement of the law. Huggins finds it "perplexing" and asks the Court not to consider the statements he made to the FDA during the 2004 inspection, in determining his sentence, citing Federal Rule of Criminal Procedure 32(i)(3)(B). But it is obvious that the Court may take all relevant conduct into account, and equally obvious that false statements made after wrongful conduct may be especially enlightening when determining the nature and character of the defendants and the additional § 3553 factors.[58] For the reasons stated at length at pages 9 through 13 of the Government's Amended Pretrial Memorandum, these objections are meritless and should be rejected.

33. Paragraphs 55 - 58 of the Presentence Reports

These paragraphs discuss the adjustment for acceptance of responsibility, concluding that none of the defendants qualify for that adjustment, because they have not admitted any relevant conduct.

Predictably, all four defendants object, stating that they need not admit to any relevant conduct now. They argue that the acceptance credit should not be denied them unless and until the Court has found that the relevant conduct is true. At that point, they claim, they may not falsely deny or frivolously contest relevant conduct that the Court has determined to be true. However, they argue, even then they may stand mute and still receive credit for acceptance. So it appears that the defendants are still deciding. This may explain Huggins' argument that the Court is not legally required to resolve factual disputes concerning offense conduct – it may

[58] Under federal law, "[n]o limitation shall be placed on the information concerning the background, character, and conduct of a person convicted of an offense which a court of the United States may receive and consider for the purpose of imposing an appropriate sentence." 18 U.S.C. § 3661.

simply sentence him and the other defendants to probation after determining that the factual disputes "will not affect sentencing." Fed. R. Crim. P. 32(i)(3)(B).

The government believes that both the presentence writer and the defendants are right. Based on their many objections to the relevant conduct outlined in the PSR (a number of which appear to be frivolous), the presentence writer is correct that the defendants have not yet accepted responsibility within the meaning of U.S.S.G. § 3E1.1.[59] But, as the defendants claim, and as the presentence writer acknowledges, "the defendant has until the time of sentencing to 'clearly' acknowledge acceptance". ¶ 58.

The government would respectfully request that the Court reject the tack suggested by defendant Huggins. The government urges that the Court make the determination of what the defendants knew, when they knew it, and what they did that led to the guilty pleas of Synthes and Norian in this case.

Respectfully submitted,

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[59] The individual defendants' entitlement to a two-level reduction in sentencing level under the advisory United States Sentencing Guidelines is dependent upon their "truthfully admitting the conduct comprising the offense(s) of conviction, and truthfully admitting or not falsely denying any additional relevant conduct for which the defendant is accountable under § 1B1.3 (Relevant Conduct)." U.S.S.G. § 3E1.1, comment. (n.1(a)) (2009). Under the same provision, "a defendant who falsely denies, or frivolously contests, relevant conduct that the court determines to be true has acted in a manner inconsistent with acceptance of responsibility." Id. The defendant bears the burden of proving his entitlement to the reduction. United States v. Boone, 279 F.3d 163, 193 (3d Cir. 2002). In addition, the sentencing Court is in a unique position to evaluate a defendant's acceptance of responsibility. Id. (quoting U.S. Sentencing Guidelines Manual § 3E1.1 cmt.).; U.S.S.G. § 3E1.1, comment. (n. 4).

CERTIFICATE OF SERVICE

This is to certify that I have caused to be delivered by electronic filing to the Clerk of Court (resulting in an e-mail copy sent to counsel by the Clerk of Court), and by direct e-mail of the within document to the following:

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