IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA	:	
v.	:	**CRIMINAL NO. 09-403-03**
MICHAEL D. HUGGINS	:	

GOVERNMENT'S GUILTY PLEA MEMORANDUM

I. INTRODUCTION

On June 16, 2009, a grand jury sitting in the Eastern District of Pennsylvania returned a 97-count indictment against the defendant, MICHAEL D. HUGGINS ("HUGGINS"), as well as three other individuals and two corporations. The indictment charges defendant Synthes, Incorporated ("Synthes"), a major medical device manufacturer which employed HUGGINS from late 1994 until January 2008, with 44 misdemeanor counts of introducing into interstate commerce adulterated and misbranded medical devices, in violation of Title 21, United States Code, Sections 331(a), 352(f)(1), 352(o), 351(f)(1)(B) and 333(a)(1). The indictment further charges defendant Norian Corporation ("Norian"), a wholly owned subsidiary of Synthes, with 52 felony violations of law. Count one alleges that defendant Norian and others participated in a dual-object conspiracy: to impair and impede the lawful functions of the Food and Drug Administration ("FDA"); and to commit offenses against the United States, all in violation of Title 18, United States Code, Section 371. Defendant Norian is further charged with 44 felony counts of introducing adulterated and misbranded medical devices into interstate commerce with the intent to defraud, in violation of Title 21, United States Code, Sections 331(a), 352(f)(1), 352(o), 351(f)(1)(B) and 333(a)(2), and seven counts of making false statements to an FDA investigator during an official inspection, in violation of Title 18, United States Code, Section

1001.

Defendant HUGGINS is charged in Count 97 of the indictment, along with three other corporate officials of defendant Synthes, with the misdemeanor offense of introduction into interstate commerce of medical devices that were adulterated pursuant to Title 21, United States Code, Section 351(f)(1)(B), and misbranded pursuant to Title 21, United States Code, Sections 352(f), (o), in violation of Title 21, United States Code, Sections 331(a) and 333(a)(1). The charge against defendant HUGGINS arises from defendants Synthes's and Norian's illegal test marketing and promotion of their medical devices Norian SRS and Norian XR in the United States between May 2002 and July 2004 and from his role as a corporate officer with responsibility to prevent such violations.

Defendant HUGGINS has notified the United States through his counsel, Gregory L. Poe, Esquire and Catherine M. Recker, Esquire, that he intends to enter a plea of guilty to count 97 of the indictment. A guilty plea hearing has been scheduled by the Court for Monday, July 20, 2009 at 10:00 a.m.

II. PLEA AGREEMENT

An executed copy of the plea agreement is attached as Exhibit A.

III. MAXIMUM PENALTIES

The statutory maximum sentence on Count 97 of the Indictment is one year of imprisonment followed by one year of supervised release, or five years of probation, a $100,000 fine, and a special assessment of $25. The Court may also order restitution and forfeiture.

IV. ELEMENTS OF THE OFFENSE

The Food, Drug and Cosmetic Act ("FDCA") prohibits introduction into interstate

commerce of any medical device which is either adulterated or misbranded. Title 21, United States Code, Section 331(a). Under Section 351 of the FDCA, a medical device is adulterated under several circumstances, including when it has been introduced into interstate commerce without first obtaining premarket approval by the FDA, or when it is required to have an approved investigational device exemption ("IDE") and does not have an approved IDE in effect.[1] Title 21, United States Code, Section 351(f)(1)(B). Premarket approval can only be obtained by submitting a premarket approval ("PMA") application. Premarket approval is required if, among other things, the device is a class III device – the sort of device that is subject to the most stringent regulatory requirements – and it has not been previously approved through the premarket approval process. If the FDA has never reviewed and classified the device, or if a previously reviewed device (including a class II device) is changed or modified in a way that could significantly affect its safety or effectiveness, or has a change in intended use, the device is presumptively a class III device requiring a PMA until stated otherwise by the FDA.

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[1] There are two ways in which a medical device manufacturer may obtain the FDA's permission to market a device in the United States. The longer and usually more expensive route is premarket approval, often called "approval," obtained by means of a premarket approval ("PMA") application. The shorter and usually less expensive route is premarket notification, often called "clearance" or "510(k) approval." As part of the pre-market approval or clearance process, the FDA often requires device manufacturers to submit the results of clinical trials or investigations, that is, research involving one or more human subjects to determine the safety of effectiveness of the device.

Manufacturers of significant risk devices cannot legally conduct clinical trials or investigations in the United States without first obtaining the FDA's permission to do so, by way of an Investigational Device Exemption ("IDE"). Before beginning a clinical trial of a significant risk device, the device manufacturer is required to obtain the FDA's approval of the IDE, and a multi-disciplinary group of professionals with backgrounds in areas like science, medicine and bioethics called an Institutional Review Board ("IRB") is required to approve the investigational plan and informed consent form, so that the clinical trial is properly monitored and the human subjects properly protected.

Introduction of an adulterated device into interstate commerce is either a misdemeanor or a felony violation of the FDCA. Misdemeanor liability is strict; no proof of intent is required. Title 21, United States Code, Section 333(a)(1). A felony conviction requires either proof of an intent to defraud or mislead, or a prior conviction under § 333. Title 21, United States Code, Section 333(a)(2).

In order to prove the crime of misdemeanor adulteration, the government must establish the following elements beyond a reasonable doubt:

(1) that Norian XR is a medical device

(2) that Norian XR was adulterated, in that it

(a) had been introduced into interstate commerce without first obtaining premarket approval by the FDA, or

(b) it was required to have an approved IDE and did not have an approved IDE in effect; and

(3) that Norian XR was introduced into interstate commerce.

Under section 352 of the FDCA, a device is "misbranded" under several circumstances, including when its label does not bear adequate directions for its intended use, and when the device manufacturer has failed to provide the FDA with pre-market notification of a new or non-FDA-cleared intended use ninety days prior to introducing the device into interstate commerce for such use. Title 21, United States Code, Section 352(f), (o).

Like the crime of adulteration, introduction of a misbranded device into interstate commerce can be either a misdemeanor or a felony violation of the FDCA. Misdemeanor liability is strict; no proof of intent is required. Title 21, United States Code, Section 333(a)(1).

A felony conviction requires either proof of an intent to defraud or mislead, or a prior conviction under § 333. Title 21, United States Code, Section 333(a)(2).

In order to prove the crime of misdemeanor misbranding, the government must establish the following elements beyond a reasonable doubt:

(1) that Norian XR is a medical device

(2) that Norian XR was misbranded, in that

(a) it lacked adequate directions for the use intended by Norian and Synthes (that is, the treatment of VCFs), or

(b) Norian and Synthes failed to provide the FDA with pre-market notification of a new or non-FDA-cleared intended use 90 days prior to introducing the device into interstate commerce for such use (that is, the treatment of VCFs), and

(3) that Norian XR was introduced into interstate commerce.

For a corporate official to be found guilty of a misdemeanor violation of the FDCA committed by his or her employer, the government must prove the following elements:

(1) that the defendant had, by reason of his or her position in the corporation, responsibility and authority either to prevent in the first instance, or to promptly correct, the criminal violation; and

(2) that the defendant failed to do so.

United States v. Park, 421 U.S. 658, 673-4 (1975).

V. SENTENCING GUIDELINES

The Sentencing Guidelines, which are now advisory, apply to this case. In the

plea agreement, the parties made two Sentencing Guidelines stipulations, outlined below. The plea agreement provides that the parties are free to argue the applicability of any other provisions of the Sentencing Guidelines, including offense conduct, offense characteristics, criminal history, adjustments and departures, and that the stipulations do not bind the Court and do not bind the Probation Department (Exhibit A, ¶ 11, pp. 8-9).

First, the parties agree to disagree concerning whether U.S.S.G. §§ 2N2.1(a) or 2X5.2 applies in this case. Second, the parties agree that, as of the date that the plea agreement was signed, the defendant had demonstrated acceptance of responsibility for his offense, making the defendant eligible for a 2-level downward adjustment under U.S.S.G. § 3E1.1(a).

VI. SUMMARY OF EVIDENCE

A. The Ultimate Facts to Which HUGGINS Stipulated in his Plea Agreement

In paragraph 9 of his plea agreement, pages 4 through 8, HUGGINS stipulated that if his case had gone to trial, the United States would have proven the following ultimate facts with regard to the conduct of Synthes:

a. The individual defendants, by virtue of their respective positions, were "responsible corporate officers" at various time during the events described below.

b. Synthes and its subsidiary, Norian marketed Norian SRS and Norian XR, each of which was a medical device within the meaning of 21 U.S.C. § 321(h)(1), and a significant risk device within the meaning of 21 C.F.R. § 812(m)(1).

c. Significant risk devices cannot be clinically tested without prior approval of the FDA, which approval is given through an investigational device exemption (IDE).

d. In the context of medical devices, clinical testing means research on one or more human

subjects to determine the safety or effectiveness of the device.

e. Shipments of a medical device in interstate commerce must be accompanied by labeling bearing adequate directions for use for each of the medical device's intended uses. A manufacturer cannot market its device for a new intended use without notifying the FDA via a new 510(k) premarket notification. The failure to notify the FDA of a new intended use misbrands the device.

f. In December 2001, Norian SRS, a calcium phosphate compound, was cleared via the 510(k) process by the FDA as a bone void filler, to fill only those bony voids that were not intrinsic to the stability of the bony structure, in the extremities, spine and pelvis. The Norian SRS label stated further that SRS was not to be mixed with any other substance. In December 2002, the successor device, Norian XR, which consisted of calcium phosphate with barium sulfate added for extra radiopacity, was cleared via the Special 510(k) process by the FDA, also as a bone void filler, with an indication statement identical to that of SRS. The Norian XR label further contained a warning: "not intended for the treatment of vertebral compression fractures."

g. Earlier, but no later than May 2002, Synthes and Norian learned that the FDA was concerned over the imprecision of the spine indication in the then-current indication for use of bone void fillers, and that the FDA understood that some surgeons, as part of their practice of medicine, were using bone void fillers in the spine for load bearing indications. The FDA asked that Synthes and Norian -- in their pre-market notification to the FDA seeking clearance of Norian XR -- provide additional labeling for Norian XR that specified that load-bearing indications, such as vertebroplasty, were not included in

the product's indication for use. Defendants Synthes and Norian then promised the FDA that the companies would not promote Norian XR for vertebroplasty or other load-bearing indications without the appropriate regulatory authority. The FDA continued to request such labeling until Synthes submitted the warning against vertebral compression fracture ("VCF") use that became a part of the Norian XR label.

h. Between August 2002 and December 2002, Synthes and Norian trained spine surgeons to mix Norian SRS with barium sulfate and to use the resulting medical device in vertebroplasty-type surgeries to treat VCFs, notwithstanding that the label of Norian SRS stated that the product was not to be mixed with any other substance. This training of surgeons to mix Norian SRS with barium sulfate for the treatment of VCFs violated 21 U.S.C. §§ 351(f)(1)(B), 352(o) and 352(f)(1) because the mixing made SRS a new device that required premarket approval or clearance for this new intended use, and that lacked adequate directions for such use.

i. Between August 2003 and January 2004, Synthes and Norian trained spine surgeons to use Norian XR in vertebroplasty-type surgeries to treat VCFs, notwithstanding that the label of Norian XR warned that the product was not intended for treatment of VCFs. This training took place as part of a so-called "test market" for Norian XR. As part of the XR "test market," Synthes and Norian directed the Synthes Spine sales force to gather clinical data about surgeries that the "test market" surgeons performed, so that Synthes and Norian could document the results of surgeries to treat VCFs, in order to assess the risk level of using Norian XR to treat VCFs, and determine whether that risk level was too high. This unauthorized clinical testing of Norian XR for the treatment of VCFs

violated 21 U.S.C. § 351(f)(1) because such testing of a significant risk device required the prior approval of the FDA, through an IDE.

j. Between December 2002 and January 2004, Synthes and Norian promoted Norian XR for use in vertebroplasty-type surgeries to treat VCFs, nothwithstanding that the label of Norian XR warned that the product was not intended for treatment of VCFs. The promotion of Norian XR for this additional intended use violated 21 U.S.C. § 351(f)(1), because Norian XR's labeling did not bear adequate directions for each of the device's intended uses, and in fact, warned against the intended use of treating VCFs.

B. The Evidence That The Government Would Introduce At Trial To Prove Those Ultimate Facts

1. Defendant HUGGINS's Positions At Synthes

The evidence would show that defendant MICHAEL HUGGINS was hired by defendant Synthes at the end of 1994, and held the following positions from 1999 through 2005, the time period covered by the indictment:

1999 through January 2004: President of Synthes North America;

February 2004 through the end of 2005: President of Synthes Spine Division.

Personnel records and testimony would show that out of the four individual defendants, HUGGINS was the highest-ranking. Further, the evidence would show that of the other three individuals defendants, Thomas Higgins reported directly to defendant HUGGINS from 1999 until February 2004; Richard Bohner reported directly to defendant HUGGINS until February 2004; and John Walsh reported to defendant HUGGINS indirectly, through Bohner, from August 2003 until February 2004, and then directly to defendant HUGGINS beginning in February 2004.

2. The Medical Context

At trial, the government would prove that vertebral compression fractures ("VCFs") are fractures of the spine, most of which result from osteoporosis. An estimated 700,000 VCFs occur annually in the United States due to osteoporosis, and a large proportion of VCFs are painful and clinically diagnosed. The aging of the baby boomer generation makes the market for treatment of VCFs a large and lucrative one.

In the 1980s, a surgery called vertebroplasty was developed to treat VCFs. During the surgery, a needle was inserted into the fractured vertebra through the back of the patient under general or local anesthesia with the help of image guided X-ray. Through the needle, the surgeon injected a mixture of bone cement and a contrast agent into the vertebral body, in order to stabilize the fractured bone and alleviate back pain.

Traditional vertebroplasty involved a high-pressure injection of bone cement. Kyphoplasty was a later variation on vertebroplasty in which a surgical instrument and a balloon were inserted into the compressed vertebral body, in order to create a cavity that elevated or expanded the fractured vertebra to its original shape. Once the instrument was withdrawn, the cavity created was then filled with bone cement under lower pressure than required for traditional vertebroplasty.

In addition to describing a traditional high-pressure injection, the term "vertebroplasty" is commonly used in a broader sense , to refer to any surgery – including those involving a created vertebral cavity – in which bone cement is injected through a needle into the vertebral body in order to stabilize the fractured bone and alleviate back pain. The evidence would show that defendants Synthes and Norian and their employees often used the term

"vertebroplasty" in this broader sense.

3. Synthes and Norian's Development and Marketing of Norian SRS and XR for Treatment of Vertebral Compression Fractures

Defendant Synthes purchased defendant Norian in mid-1999. At that time, Norian manufactured and marketed two bone cements: SRS, which stands for Skeletal Repair System, and CRS, which stands for Cranial Repair System. Beginning in spring 2000, defendants Synthes and Norian conducted market research on the use of Norian bone cements to treat VCFs, and interviewed spine surgeons, neuroradiologists, and neurosurgeons who used an acrylic bone cement, polymethylmethacrylate ("PMMA"), off-label in vertebroplasty and kyphoplasty surgeries to treat VCFs. Defendants Synthes and Norian asked them whether they had used SRS in such surgeries, how SRS had performed in this indication, how to improve the use of SRS in such surgeries, and – for the many surgeons who had used only PMMA – how often they might use SRS in such surgeries, among other questions. 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.

In November 2001, at a management meeting attended by defendants HUGGINS and Higgins and other top Synthes officials, 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. After this meeting, the CEO and major shareholder of Synthes directed that Synthes would not pursue FDA approval of Norian via an IDE and a PMA, but instead would press on

with a "test market"[2] 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. Defendant 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. Documentary evidence and testimony would show that no later than May 2002, defendant HUGGINS was aware of, and involved in, the process of approving the SRS test market in the spine.

On December 20, 2001, defendant Synthes 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. Defendant Synthes never told the FDA that it intended to market SRS for load-bearing spine use such as treating VCFs.

By May 2002, defendants Synthes and Norian had had multiple conversations with the FDA about CRS and SRS. Through those conversations, starting as early as 1999, defendants Synthes and Norian had become aware of the FDA's concerns with the products, and in particular, that the FDA was concerned about their use in the vertebral bodies.

Specifically, on May 8, 2002, defendants Synthes and Norian had a telephone conference call with the FDA concerning the new SRS plus barium sulfate (the product

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[2] "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*. In this case, however, both the SRS test market in the spine and the later XR test market were for the *unapproved* indication of treatment of VCFs.

eventually named XR). During the call, the FDA stated that it was concerned about the imprecision in the current indication for use, and that it understood that as part of their practice of medicine, surgeons were using bone void fillers in the spine for load bearing indications. The FDA asked that defendants Synthes and Norian provide additional labeling for XR that specified that load bearing indications, such as vertebroplasty, were not included in the current indication for use. Defendants Synthes and Norian promised the FDA that they would not promote XR for vertebroplasty or other load-bearing indications without the appropriate regulatory authority. The companies expressed their belief that such labeling would create an uneven playing field, as no other manufacturers of other bone void fillers had such labeling, but the FDA continued to request such labeling until defendant Synthes submitted the warning against VCF use that became part of the Norian XR label.

The trial evidence would show that when defendants Synthes and Norian made this promise to the FDA during the May 2002 conference call, their 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. Documents and other testimony would show that, prior to May 2002, this representative and others had communicated this fact to others higher up in defendant Synthes' management.

Emails and testimony would show that by May 2002, defendant Synthes's own regulatory employees had also given Synthes notice, and to spare, that promoting use of SRS to treat VCFs was illegal. Other Synthes employees, from other departments, made this point even clearer later, in December 2002, going so far as to say that if there was any doubt, the opinion of counsel should be sought on the question. So far as the evidence shows, counsel was not

consulted until after the third patient death.

Defendant Synthes also received notice through the FDA's statements to other companies, 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. Defendant Synthes also received notice from the FDA's public pronouncements, or web alerts, publicizing complications that had been reported related to vertebroplasty-type surgeries to treat VCFs. One web alert in October 2002, updated later, warned that the reported complications were related to the leakage of PMMA during surgeries to treat VCFs.

Thus, the evidence would show that, as time went on, defendants Synthes and Norian were increasingly on notice that the Norian bone void fillers might pose serious risks if used in the spine in humans, specifically:

-- 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. Defendant Synthes learned that Doctor No. 1 had previously performed about 50 VCF surgeries with PMMA without incident. Defendant Synthes filed Medical Device Reports ("MDRs") on the two Doctor No. 1 hypotensive

events.[3] Documents would show that subordinates informed defendant HUGGINS of the two Doctor No. 1 hypotensive events, and that in response, HUGGINS directed subordinates to reel in the sales force "ASAP" concerning the use of CRS in VCF surgeries.

-- at a meeting called by defendant Synthes with surgeons and researchers to try to learn the cause(s) of the Doctor No. 1 hypotensive events, one participant, 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 defendant 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, defendant 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.

-- 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.

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[3] By regulation, a device manufacturer must file an MDR with the FDA within 30 days, whenever the manufacturer learns information from any source that reasonably suggests that the manufacturer's device might have caused or contributed to a death or serious injury.

-- in May and June 2002, Doctor No. 2 and his partner, identified in the indictment as Doctor No. 3, told defendant 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 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.

At the end of May 2002, 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 Synthes and Norian approved the SRS test market in the spine, in which the companies taught spine surgeons how to mix SRS with barium sulfate and use it in surgeries to treat VCFs. The evidence would show that prior to approval of the SRS test market in the spine, defendant HUGGINS was in contact with a medical consultant for defendant Synthes who opposed the SRS test market in the spine, warning that it amounted to human experimentation. The evidence would show that, on May 30, 2002, after speaking with the medical 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 Exhibit B. Nonetheless, documents and testimony

would 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. The progress of the SRS test market in the spine was discussed at a management meeting in September 2002, attended by defendant HUGGINS and others. The results of the SRS test market in the spine were also discussed later at the July 18, 2003 Safety Meeting and in the Safety meeting materials, Exhibit C, see pages 19-20, below.

In fall 2002, defendant Synthes submitted to the FDA a Special 510(k)[4] 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 defendants 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. And defendant 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.

On December 16, 2002, defendant Synthes learned that the FDA was still seeking specific wording concerning "no vertebroplasty and non load bearing only"; two days later, Synthes agreed to add the warning "not intended for treatment of [VCFs]" to the XR label.

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

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[4] A "Special 510(k)" is available to manufacturers who are seeking to market a modified version of their own previously-cleared device. The regulations are 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.

intrinsic to the stability of the bony structure" in the extremities, spine and pelvis, and specifically warning that XR was "not intended for treatment of vertebral compression fractures."

Less than a month later, 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's cavity creation instruments to treat VCFs. That surgeon is identified in the indictment as Doctor No. 4. The proof would show that a Synthes sales consultant was present during the surgery and that the SRS was mixed with barium sulfate in the consultant's presence. After suffering a hypotensive episode, Doctor No. 4's patient died on the operating table ("the first death"). In conversations with three Synthes Spine employees, Doctor No. 4 did not rule out the mixed SRS as a cause of the first death.

Even though Doctor No. 4 could not rule out SRS as a cause of the first death, defendants Synthes and Norian made the decision not to file an MDR on that death. In addition, neither company had an independent medical expert review the death.

In late January 2003, following the first death, defendant Richard Bohner emailed defendant Thomas Higgins, with a copy to defendant 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, Bohner 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

defendant HUGGINS, however, no communication that included both the warning label for XR and an admonition that XR should not be promoted for off-label use was sent to the Spine sales force.

In late February 2003, a Synthes regulatory employee 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, 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.

On July 18, 2003, defendants Synthes and Norian held a "Safety Meeting" attended by defendants HUGGINS, Higgins, Bohner and others. Documents and participant testimony would show that defendant HUGGINS was the most senior manager present at the Safety Meeting. According to the materials distributed at the Safety Meeting, the declared purpose of the meeting was to decide whether Norian XR was safe enough to bring to market. Safety Meeting participants heard a presentation by the XR product manager on the pilot studies, the two adverse hypotensive events that had occurred with Doctor No. 1's patients, and the first death. Notes from the meeting show that the participants also discussed defendant Synthes's 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 VCF cases to date (a

statistically significant figure). Faced with the choice whether to seek an IDE and a PMA, defendants Synthes and Norian decided to continue the XR "test market" for use in vertebroplasty 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 at the Safety Meeting are attached as Exhibit C; the minutes of the Safety Meeting, which show that defendant HUGGINS received them, are attached as Exhibit D.

In August 2003, defendants HUGGINS and Higgins, other employees and a number of surgeons held a strategic planning meeting on XR, at which the issue of an approved clinical study of XR was raised again. The meeting minutes and participant testimony would show that defendant HUGGINS noted that Synthes had a "poor record of PMA approvals," and that 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.

On August 15 and 16, 2003, defendants Synthes and Norian held the first surgeon training meeting of the test market, at which 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, the companies distributed notebooks to the attending spine surgeons which thanked them for participating in the XR "test market," and gave the sales consultants forms[5] for

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[5] The information that Synthes 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 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.

reordering XR ("test market reorder forms" or "TM forms"). Defendant Synthes also instructed its sales consultants, 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, the companies did not inform the trainee surgeons of the first death, the other adverse events, or the pilot study results.

On September 19, 2003, when a spine surgeon, 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"). The proof would show that a Synthes sales consultant was present during the surgery. 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. Defendants 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.

Despite the second death, defendants Synthes and Norian continued the second surgeon training meeting of the "test market" on September 19 and 20, 2003. The second training followed a format identical in substance to the first surgeon training, and again included spine surgeons selected by defendant Synthes based on their experience in performing vertebroplasty, and whose expenses to travel to and attend the training were paid for by defendant Synthes. At the second surgeon training, defendant Synthes did not inform 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).

Only days later, a spine surgeon identified in the indictment as Doctor No. 6 told defendant Synthes 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 defendant Synthes was required to go to each institutional review board ("IRB") of each hospital participating in the "test market." Doctor No. 6 also told defendant Synthes 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." Doctor No. 6 also told defendant Synthes that, in his view, Synthes had risk management problems and needed more oversight of its clinical and compliance issues. The evidence would show that defendant HUGGINS was informed of Doctor No. 6's views, and also that defendant HUGGINS was the most senior manager present at meetings following the death of Dr. 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.

In November 2003, while the Norian XR test market continued, defendant Synthes gave the four individual defendants an initial proposal for obtaining an IDE so that Synthes, like one of its competitors had recently done, might seek permission to conduct clinical trials of its bone void filler in vertebroplasty surgeries for the treatment of VCFs ("the IDE proposal"). This proposal was never shared with the FDA. After discussing the XR "test market" and the fact that two patient deaths had occurred as part of the "test market," the IDE proposal discussed competitive activity with other products, stating that XR was the only product

that the FDA required to add the warning bullet. "From 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." The IDE proposal went on to state:

> **Currently, Norian XR is being used off-label to treat VCFs.** The FDA has been very conservative regarding the treatment of VCFs and has issued numerous statements . . .cautioning companies . . . that the use of any material in vertebroplasty/kyphoplasty is off-label. The present state of the approved indication of Norian XR and the FDA bulletin puts Synthes in a compromising position. Synthes is at an increased legal risk with regards to product liability and medical malpractice . . . We recommend that Synthes pursue an IDE for the usage of Norian XR in treating VCFs. . . (Emphasis supplied).

At the end of December 2003, defendant John 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 notwithstanding 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. Also at the end of December 2003, Synthes released XR for sale beyond the original "test market."

On January 10 and 11, 2004, defendants Synthes and Norian 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]. The trial evidence would show that Doctor No. 4 re-worded the warning, which led to questions from the surgeons in attendance. The evidence would show that the company representatives did nothing to dispel any confusion that Doctor No. 4's presentation may have caused. In addition, the XR Technique Guide went to all attendees,

including the 30 surgeons.

On January 22, 2004, a spine surgeon identified in the indictment as Doctor No. 7 (who at the time was Doctor No. 6's partner) 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 ("the third death"). Doctor No. 7 could not rule out Norian XR as a cause of the third death. Once again, a sales consultant was present in the operating room during the surgery that resulted in the third death. Although defendants Synthes and Norian filed an MDR on the third death, that MDR was vague as to the surgery and its details. Moreover, defendants 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.

After the third death, defendants Synthes and Norian 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, defendants Synthes and Norian left XR on the market, and sent surgeons a misleading "dear surgeon" letter, signed by defendant HUGGINS in 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," while remaining silent about the warning bullet, and further omitted to state that:

-- Synthes had conducted a "test market" in which it had trained surgeons to use XR to treat VCFs;

-- the pilot studies indicated that Norian appeared to be a thrombogenic agent;[6] and

-- three patients had died on the operating table when spine surgeons had used Norian XR or its predecessor, SRS, off-label to treat VCFs.

The "dear surgeon" letter is attached as Exhibit E. The "dear surgeon" letter proves that defendant Synthes and defendant HUGGINS well understood the indication statement on the XR label, what it allowed and did not allow, and how narrow that indication statement really was.[7]

The United States respectfully submits that this summary of evidence provides a factual basis for the guilty plea by Michael D. Huggins to Count 97 of the indictment.

Respectfully submitted,

MICHAEL L. LEVY
United States Attorney

MARY E. CRAWLEY
GERALD B. SULLIVAN
DAVID J. CAPUTO
Assistant United States Attorney

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

[7] At trial, under Rule 404(b), Fed.R.Evid., the government would also introduce evidence that during an unannounced FDA inspection of defendants Norian and Synthes in May and June 2004, a number of individuals including defendant HUGGINS made false statements to the FDA investigator, on behalf of defendants Norian and Synthes.

CERTIFICATE OF SERVICE

I hereby certify that I have caused to be served a true and correct copy of the annexed Guilty Plea Memorandum on counsel for the defendant **MICHAEL D. HUGGINS**, by electronic filing:

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MARY E. CRAWLEY
Assistant United States Attorney

DATE: 7/16/09

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA	**:**	
v.	**:**	**CRIMINAL NO. 09-403-06**
JOHN J. WALSH	**:**	

GOVERNMENT'S GUILTY PLEA MEMORANDUM

I. INTRODUCTION

On June 16, 2009, a grand jury sitting in the Eastern District of Pennsylvania returned a 97-count indictment against the defendant, JOHN J. WALSH ("WALSH"), as well as three other individuals and two corporations. The indictment charges defendant Synthes, Incorporated ("Synthes"), a major medical device manufacturer by whom WALSH is employed, with 44 misdemeanor counts of introducing into interstate commerce adulterated and misbranded medical devices, in violation of Title 21, United States Code, Sections 331(a), 352(f)(1), 352(o), 351(f)(1)(B) and 333(a)(1). The indictment further charges defendant Norian Corporation ("Norian"), a wholly owned subsidiary of Synthes, with 52 felony violations of law. Count one alleges that defendant Norian and others participated in a dual-object conspiracy: to impair and impede the lawful functions of the Food and Drug Administration ("FDA"); and to commit offenses against the United States, all in violation of Title 18, United States Code, Section 371. Defendant Norian is further charged with 44 felony counts of introducing adulterated and misbranded medical devices into interstate commerce with the intent to defraud, in violation of Title 21, United States Code, Sections 331(a), 352(f)(1), 352(o), 351(f)(1)(B) and 333(a)(2), and seven counts of making false statements to an FDA investigator during an official inspection, in violation of Title 18, United States Code, Section 1001.

Defendant WALSH is charged in Count 97 of the indictment, along with three other corporate officials of defendant Synthes, with the misdemeanor offense of introduction into interstate commerce of medical devices that were adulterated pursuant to Title 21, United States Code, Section 351(f)(1)(B), and misbranded pursuant to Title 21, United States Code, Sections 352(f), (o), in violation of Title 21, United States Code, Sections 331(a) and 333(a)(1). The charge against defendant WALSH arises from defendants Synthes's and Norian's illegal test marketing and promotion of their medical devices Norian SRS and Norian XR in the United States between May 2002 and July 2004 and from his role as a corporate officer with responsibility to prevent such violations.

Defendant WALSH has notified the United States through his counsel, William E. Lawler, III, Esquire and Craig D. Margolis, Esquire, that he intends to enter a plea of guilty to count 97 of the indictment. A guilty plea hearing has been scheduled by the Court for Monday, July 20, 2009 at 11:00 a.m.

II. PLEA AGREEMENT

An executed copy of the plea agreement is attached as Exhibit A.

III. MAXIMUM PENALTIES

The statutory maximum sentence on Count 97 of the indictment is one year of imprisonment followed by one year of supervised release, or five years of probation, a $100,000 fine, and a special assessment of $25. The Court may also order restitution and forfeiture.

IV. ELEMENTS OF THE OFFENSE

The Food, Drug and Cosmetic Act ("FDCA") prohibits introduction into interstate commerce of any medical device which is either adulterated or misbranded. Title 21, United

States Code, Section 331(a). Under Section 351 of the FDCA, a medical device is adulterated under several circumstances, including when it has been introduced into interstate commerce without first obtaining premarket approval by the FDA, or when it is required to have an approved investigational device exemption ("IDE") and does not have an approved IDE in effect.[1] Title 21, United States Code, Section 351(f)(1)(B). Premarket approval can only be obtained by submitting a premarket approval ("PMA") application. Premarket approval is required if, among other things, the device is a class III device – the sort of device that is subject to the most stringent regulatory requirements – and it has not been previously approved through the premarket approval process. If the FDA has never reviewed and classified the device, or if a previously reviewed device (including a class II device) is changed or modified in a way that could significantly affect its safety or effectiveness, or has a change in intended use, the device is presumptively a class III device requiring a PMA until stated otherwise by the FDA.

Introduction of an adulterated device into interstate commerce is either a

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[1] There are two ways in which a medical device manufacturer may obtain the FDA's permission to market a device in the United States. The longer and usually more expensive route is premarket approval, often called "approval," obtained by means of a premarket approval ("PMA") application. The shorter and usually less expensive route is premarket notification, often called "clearance" or "510(k) approval." As part of the pre-market approval or clearance process, the FDA often requires device manufacturers to submit the results of clinical trials or investigations, that is, research involving one or more human subjects to determine the safety of effectiveness of the device.

Manufacturers of significant risk devices cannot legally conduct clinical trials or investigations in the United States without first obtaining the FDA's permission to do so, by way of an Investigational Device Exemption ("IDE"). Before beginning a clinical trial of a significant risk device, the device manufacturer is required to obtain the FDA's approval of the IDE, and a multi-disciplinary group of professionals with backgrounds in areas like science, medicine and bioethics called an Institutional Review Board ("IRB") is required to approve the investigational plan and informed consent form, so that the clinical trial is properly monitored and the human subjects properly protected.

misdemeanor or a felony violation of the FDCA. Misdemeanor liability is strict; no proof of intent is required. Title 21, United States Code, Section 333(a)(1). A felony conviction requires either proof of an intent to defraud or mislead, or a prior conviction under § 333. Title 21, United States Code, Section 333(a)(2).

In order to prove the crime of misdemeanor adulteration, the government must establish the following elements beyond a reasonable doubt:

(1) that Norian XR is a medical device

(2) that Norian XR was adulterated, in that it

(a) had been introduced into interstate commerce without first obtaining premarket approval by the FDA, or

(b) it was required to have an approved IDE and did not have an approved IDE in effect; and

(3) that Norian XR was introduced into interstate commerce.

Under section 352 of the FDCA, a device is "misbranded" under several circumstances, including when its label does not bear adequate directions for its intended use, and when the device manufacturer has failed to provide the FDA with pre-market notification of a new or non-FDA-cleared intended use ninety days prior to introducing the device into interstate commerce for such use. Title 21, United States Code, Section 352(f), (o).

Like the crime of adulteration, introduction of a misbranded device into interstate commerce can be either a misdemeanor or a felony violation of the FDCA. Misdemeanor liability is strict; no proof of intent is required. Title 21, United States Code, Section 333(a)(1). A felony conviction requires either proof of an intent to defraud or mislead, or a prior conviction

under § 333. Title 21, United States Code, Section 333(a)(2).

In order to prove the crime of misdemeanor misbranding, the government must establish the following elements beyond a reasonable doubt:

(1) that Norian XR is a medical device

(2) that Norian XR was misbranded, in that

(a) it lacked adequate directions for the use intended by Norian and Synthes (that is, the treatment of VCFs), or

(b) Norian and Synthes failed to provide the FDA with pre-market notification of a new or non-FDA-cleared intended use 90 days prior to introducing the device into interstate commerce for such use (that is, the treatment of VCFs), and

(3) that Norian XR was introduced into interstate commerce.

For a corporate official to be found guilty of a misdemeanor violation of the FDCA committed by his or her employer, the government must prove the following elements:

(1) that the defendant had, by reason of his or her position in the corporation, responsibility and authority either to prevent in the first instance, or to promptly correct, the criminal violation; and

(2) that the defendant failed to do so.

United States v. Park, 421 U.S. 658, 673-4 (1975).

V. SENTENCING GUIDELINES

The Sentencing Guidelines, which are now advisory, apply to this case. In the plea agreement, the parties made two Sentencing Guidelines stipulations, outlined below. The

plea agreement provides that the parties are free to argue the applicability of any other provisions of the Sentencing Guidelines, including offense conduct, offense characteristics, criminal history, adjustments and departures, and that the stipulations do not bind the Court and do not bind the Probation Department (Exhibit A, ¶ 11, pp. 8-9).

First, the parties agree to disagree concerning whether U.S.S.G. §§ 2N2.1(a) or 2X5.2 applies in this case. Second, the parties agree that, as of the date that the plea agreement was signed, the defendant had demonstrated acceptance of responsibility for his offense, making the defendant eligible for a 2-level downward adjustment under U.S.S.G. § 3E1.1(a).

VI. SUMMARY OF EVIDENCE

A. The Ultimate Facts to Which WALSH Stipulated in his Plea Agreement

In paragraph 9 of his plea agreement, pages 4 through 8, WALSH stipulated that if his case had gone to trial, the United States would have proven the following ultimate facts with regard to the conduct of Synthes:[2]

a. The individual defendants, by virtue of their respective positions, were "responsible corporate officers" at various time during the events described below.

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[2] The United States notes that, unlike the other three individual defendants, Huggins, Higgins and Bohner, who were long-time Synthes officials, WALSH began working at Synthes in 2003, after the development of XR for the treatment of VCFs; after the illegal SRS test market in spine; and after Synthes had sought and obtained 510(k) clearance for Norian XR as a 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 intended for treatment of vertebral compression fractures." Thus, a portion of the evidence that the United States would introduce at trial concerns events predating WALSH's tenure at Synthes. The evidence that predates WALSH's tenure at Synthes is summarized at pages 11- 18 below, not because WALSH was responsible for preventing that part of Synthes's and Norian's crimes – he was not – but because, in the government's view, it is necessary to an understanding of the events that followed, that happened on WALSH's watch.

b. Synthes and its subsidiary, Norian marketed Norian SRS and Norian XR, each of which was a medical device within the meaning of 21 U.S.C. § 321(h)(1), and a significant risk device within the meaning of 21 C.F.R. § 812(m)(1).

c. Significant risk devices cannot be clinically tested without prior approval of the FDA, which approval is given through an investigational device exemption (IDE).

d. In the context of medical devices, clinical testing means research on one or more human subjects to determine the safety or effectiveness of the device.

e. Shipments of a medical device in interstate commerce must be accompanied by labeling bearing adequate directions for use for each of the medical device's intended uses. A manufacturer cannot market its device for a new intended use without notifying the FDA via a new 510(k) premarket notification. The failure to notify the FDA of a new intended use misbrands the device.

f. In December 2001, Norian SRS, a calcium phosphate compound, was cleared via the 510(k) process by the FDA as a bone void filler, to fill only those bony voids that were not intrinsic to the stability of the bony structure, in the extremities, spine and pelvis. The Norian SRS label stated further that SRS was not to be mixed with any other substance. In December 2002, the successor device, Norian XR, which consisted of calcium phosphate with barium sulfate added for extra radiopacity, was cleared via the Special 510(k) process by the FDA, also as a bone void filler, with an indication statement identical to that of SRS. The Norian XR label further contained a warning: "not intended for the treatment of vertebral compression fractures."

g. Earlier, but no later than May 2002, Synthes and Norian learned that the FDA was

concerned over the imprecision of the spine indication in the then-current indication for use of bone void fillers, and that the FDA understood that some surgeons, as part of their practice of medicine, were using bone void fillers in the spine for load bearing indications. The FDA asked that Synthes and Norian -- in their pre-market notification to the FDA seeking clearance of Norian XR -- provide additional labeling for Norian XR that specified that load-bearing indications, such as vertebroplasty, were not included in the product's indication for use. Defendants Synthes and Norian then promised the FDA that the companies would not promote Norian XR for vertebroplasty or other load-bearing indications without the appropriate regulatory authority. The FDA continued to request such labeling until Synthes submitted the warning against vertebral compression fracture ("VCF") use that became a part of the Norian XR label.

h. Between August 2002 and December 2002, Synthes and Norian trained spine surgeons to mix Norian SRS with barium sulfate and to use the resulting medical device in vertebroplasty-type surgeries to treat VCFs, notwithstanding that the label of Norian SRS stated that the product was not to be mixed with any other substance. This training of surgeons to mix Norian SRS with barium sulfate for the treatment of VCFs violated 21 U.S.C. §§ 351(f)(1)(B), 352(o) and 352(f)(1) because the mixing made SRS a new device that required premarket approval or clearance for this new intended use, and that lacked adequate directions for such use.

i. Between August 2003 and January 2004, Synthes and Norian trained spine surgeons to use Norian XR in vertebroplasty-type surgeries to treat VCFs, notwithstanding that the label of Norian XR warned that the product was not intended for treatment of VCFs.

This training took place as part of a so-called "test market" for Norian XR. As part of the XR "test market," Synthes and Norian directed the Synthes Spine sales force to gather clinical data about surgeries that the "test market" surgeons performed, so that Synthes and Norian could document the results of surgeries to treat VCFs, in order to assess the risk level of using Norian XR to treat VCFs, and determine whether that risk level was too high. This unauthorized clinical testing of Norian XR for the treatment of VCFs violated 21 U.S.C. § 351(f)(1) because such testing of a significant risk device required the prior approval of the FDA, through an IDE.

j. Between December 2002 and January 2004, Synthes and Norian promoted Norian XR for use in vertebroplasty-type surgeries to treat VCFs, nothwithstanding that the label of Norian XR warned that the product was not intended for treatment of VCFs. The promotion of Norian XR for this additional intended use violated 21 U.S.C. § 351(f)(1), because Norian XR's labeling did not bear adequate directions for each of the device's intended uses, and in fact, warned against the intended use of treating VCFs.

B. The Evidence That The Government Would Introduce At Trial To Prove Those Ultimate Facts

1. Defendant WALSH's Positions At Synthes

The evidence would show that defendant WALSH was hired by defendant Synthes as a regulatory consultant in the Spine Division in June 2003; he became employed full time at Synthes in August 2003, with the title Director of Regulatory and Clinical Affairs in the Spine Division. Personnel records and testimony would show that WALSH reported to defendant Richard Bohner from August 2003 until February 2004, and then to defendant Michael

Huggins beginning in February 2004.

2. The Medical Context

At trial, the government would prove that vertebral compression fractures ("VCFs") are fractures of the spine, most of which result from osteoporosis. An estimated 700,000 VCFs occur annually in the United States due to osteoporosis, and a large proportion of VCFs are painful and clinically diagnosed. The aging of the baby boomer generation makes the market for treatment of VCFs a large and lucrative one.

In the 1980s, a surgery called vertebroplasty was developed to treat VCFs. During the surgery, a needle was inserted into the fractured vertebra through the back of the patient under general or local anesthesia with the help of image guided X-ray. Through the needle, the surgeon injected a mixture of bone cement and a contrast agent into the vertebral body, in order to stabilize the fractured bone and alleviate back pain.

Traditional vertebroplasty involved a high-pressure injection of bone cement. Kyphoplasty was a later variation on vertebroplasty in which a surgical instrument and a balloon were inserted through a needle hole into the compressed vertebral body, in order to create a cavity that elevated or expanded the fractured vertebra to its original shape. Once the instrument was withdrawn, the cavity created was filled with bone cement under lower pressure than required for traditional vertebroplasty.

In addition to describing a traditional high-pressure injection procedure, the term "vertebroplasty" is commonly used in a broader sense to refer to any minimally invasive surgery – including those involving a created vertebral cavity – in which bone cement is injected through a needle into the vertebral body in order to stabilize the fractured bone and alleviate back pain.

The evidence would show that defendants Synthes and Norian and their employees often used the term "vertebroplasty" in this broader sense.

3. Synthes's and Norian's Development and Marketing of Norian SRS and XR for Treatment of Vertebral Compression Fractures

Defendant Synthes purchased defendant Norian in mid-1999. At that time, Norian manufactured and marketed two bone cements: SRS, which stands for Skeletal Repair System; and CRS, which stands for Cranial Repair System. Beginning in spring 2000, defendants Synthes and Norian conducted market research on the use of Norian bone cements to treat VCFs, and interviewed spine surgeons, neuroradiologists, and neurosurgeons who used an acrylic bone cement, polymethylmethacrylate ("PMMA"), off-label in vertebroplasty and kyphoplasty surgeries to treat VCFs. Defendants Synthes and Norian asked them whether they had used SRS in such surgeries, how SRS had performed in this indication, how to improve the use of SRS in such surgeries, and – for the many surgeons who had used only PMMA – how often they might use SRS in such surgeries, among other questions. 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, at a time when there was little-to-no such use of Norian cements in the United States for such procedures, in which PMMA was almost exclusively used.

In November 2001, at a management meeting attended by defendants Huggins, Higgins and other top Synthes officials, 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. After

this meeting, the CEO and major shareholder of Synthes directed that Synthes would not pursue FDA approval for vertebral use of Norian via an IDE and a PMA, but instead would press on with a "test market"[3] 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. Defendant 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.

On December 20, 2001, defendant Synthes 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. Defendant Synthes never told the FDA that it intended to market SRS for load-bearing spine use such as treating VCFs.

By May 2002, defendants Synthes and Norian had had multiple conversations with the FDA about CRS and SRS. Through those conversations, starting as early as 1999, defendants Synthes and Norian had become aware of the FDA's concerns with the products, and in particular, that the FDA was concerned about their use in vertebral bodies.

Specifically, on May 8, 2002, defendants Synthes and Norian had a telephone conference call with the FDA concerning the new SRS plus barium sulfate (the product eventually named XR). During the call, the FDA stated that it was concerned about a possible

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[3] "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*. In this case, however, both the SRS test market in the spine and the later XR test market were for the *unapproved* indication of treatment of VCFs.

perception of imprecision in the current indication for use because it referred to the spine, and that it understood that as part of their practice of medicine surgeons were using bone void fillers in the spine for load bearing indications. The FDA asked that defendants Synthes and Norian provide additional labeling for XR that specified that load bearing indications, such as vertebroplasty, were not included in the current indication for use. Defendants Synthes and Norian promised the FDA that they would not promote XR for vertebroplasty or other load-bearing indications without the appropriate regulatory authority. The companies expressed their belief that such labeling would create an uneven playing field, as no other manufacturers of other bone void fillers had such labeling, but the FDA continued to request such labeling until defendant Synthes submitted the warning against VCF use that became part of the Norian XR label.

Emails and testimony would show that, by May 2002, defendant Synthes's own regulatory employees had given Synthes notice, and to spare, that promoting use of SRS to treat VCFs was illegal. Other Synthes employees, from other departments, made this point even clearer later, in December 2002, going so far as to say that if there was any doubt, the opinion of counsel should be sought on the question. So far as the evidence shows, counsel was not consulted until after the third patient death.

Defendant Synthes also received notice through the FDA's statements to other companies, including 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. Defendant Synthes also received notice from the FDA's public pronouncements, or web alerts, publicizing complications that had been reported related to vertebroplasty-type surgeries to treat VCFs. One

web alert in October 2002, updated later, warned that the reported complications were related to the leakage of PMMA during surgeries to treat VCFs.

The evidence would show that, as time went on, defendants Synthes and Norian were increasingly on notice that the Norian bone void fillers in particular – as contrasted with PMMA and other bone void fillers – might pose uniquely serious risks if used in the spine in humans, specifically:

-- 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 consultant, 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. Defendant Synthes learned that Doctor No. 1 had previously performed about 50 VCF surgeries with PMMA without incident. Defendant Synthes filed Medical Device Reports ("MDRs") on the two Doctor No. 1 hypotensive events.[4]

-- at a meeting called by defendant Synthes with surgeons and researchers to try to learn the cause(s) of the Doctor No. 1 hypotensive events, one participant, 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

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[4] By regulation, a device manufacturer must file an MDR with the FDA within 30 days, whenever the manufacturer learns information from any source that reasonably suggests that the manufacturer's device might have caused or contributed to a death or serious injury.

causing problems. He told defendant 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, defendant 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.

-- 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 as Doctor No. 3, told defendant 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 the SRS formulation 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 following injection of SRS. The surgeons also reported some of their findings from their pilot studies with SRS to the FDA via an MDR.

At the end of May 2002, notwithstanding the growing awareness of the serious risks uniquely 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 Synthes and Norian approved the SRS test market in the spine, in which the companies taught spine surgeons how to mix SRS with barium sulfate and use it in surgeries to treat VCFs. The evidence would show that, prior to approval of the SRS test market in the spine, defendant Huggins was in contact with a medical consultant for defendant Synthes who opposed the SRS test market in the spine, warning that it amounted to human experimentation. The evidence would show that, on May 30, 2002, after speaking with the medical 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. Nonetheless, documents and testimony would 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. The progress of the SRS test market in the spine was discussed at a management meeting in September 2002; the results of the SRS test market in the spine were also discussed later at the July 18, 2003 Safety Meeting and in the Safety meeting materials.

In fall 2002, defendant Synthes submitted to the FDA a Special 510(k)[5] premarket notification for XR requesting clearance for a general bone void filler indication, listing Norian

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[5] A "Special 510(k)" is available to manufacturers who are seeking to market a modified version of their own previously cleared device. The regulations are 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.

as the manufacturer, and telling the FDA that XR was substantially equivalent to SRS. Notwithstanding the promise that defendants 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. And defendant Synthes never told the FDA that its true intended use for XR was to market it for load-bearing spine use – treating VCFs.

On December 16, 2002, defendant Synthes learned that the FDA was still seeking specific wording concerning "no vertebroplasty and non load bearing only"; two days later, Synthes agreed to add the warning "not intended for treatment of [VCFs]" to the XR label.

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 intended for treatment of vertebral compression fractures."

Less than a month later, 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's cavity creation instruments to treat VCFs. That surgeon is identified in the indictment as Doctor No. 4. The proof would show that a Synthes sales consultant was present during the surgery and that the SRS was mixed with barium sulfate in the consultant's presence. After suffering a hypotensive episode, Doctor No. 4's patient died on the operating table ("the first death"). In conversations with three Synthes Spine employees, Doctor No. 4 did not rule out the mixed SRS as a cause of the first death.

Even though Doctor No. 4 could not rule out SRS as a cause of the first death,

defendants Synthes and Norian made the decision not to file an MDR on that death. In addition, neither company had an independent medical expert review the death.

In late January 2003, following the first death, defendant Bohner emailed defendant Higgins, with a copy to defendant 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, Bohner 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, however, no communication that included both the warning label for XR and an admonition that XR should not be promoted for off-label use was sent to the Spine sales force.

In late February 2003, a Synthes regulatory employee 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, 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.

The evidence would show that this email was later forwarded to defendant WALSH, on October 16, 2004. See Exhibit B, attached.

On July 18, 2003, defendants Synthes and Norian held a "Safety Meeting" attended by defendants Huggins, Higgins, Bohner and others. According to the materials distributed at the Safety Meeting, the declared purpose of the meeting was to decide whether Norian XR was safe enough to bring to market. Safety Meeting participants heard a presentation by the XR product manager on the pilot studies, the two adverse hypotensive events that had occurred with Doctor No. 1's patients, and the first death. Notes from the meeting show that the participants also discussed defendant Synthes's 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 VCF cases to date (a statistically significant figure). Faced with the choice whether to seek an IDE and a PMA, defendants Synthes and Norian instead decided to stay under the FDA's radar by continuing the XR "test market" for use in vertebroplasty to treat VCFs that had begun in late summer of 2002 with SRS, with the goal of having "test sites" publish results of surgeries.

In August 2003, defendants Huggins and Higgins, other employees and a number of surgeons held a strategic planning meeting on XR, at which the issue of an approved clinical study of XR was raised again. The meeting minutes and participant testimony would show that defendant Huggins noted that Synthes had a "poor record of PMA approvals," and that 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. At trial, the

proof would show that the meeting minutes were forwarded to defendant WALSH the day after the meeting, while he was still a regulatory consultant for the Spine Division.

On August 15 and 16, 2003, defendants Synthes and Norian held the first surgeon training meeting of the XR test market, at which 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, the companies distributed notebooks to the attending spine surgeons which thanked them for participating in the XR "test market," and gave the sales consultants forms[6] for reordering XR ("test market reorder forms" or "TM forms"). Defendant Synthes also instructed its sales consultants, 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, the companies did not inform the trainee surgeons of the first death, the other adverse events, or the pilot study results.

The trial evidence would show that on or about August 20, 2003, defendant WALSH became a full-time Synthes employee, with the title of Director of Regulatory and Clinical Affairs in the Spine Division, reporting to defendant Bohner.

On September 19, 2003, when a spine surgeon, 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"). The proof

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[6] The information that Synthes 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 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.

would show that a Synthes sales consultant was present during the surgery. 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. Defendants 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.

Despite the second death, defendants Synthes and Norian continued the second surgeon training meeting of the "test market" on September 19 and 20, 2003. The second training followed a format identical in substance to the first surgeon training, and again included spine surgeons selected by defendant Synthes based on their experience in performing vertebroplasty, and whose expenses to travel to and attend the training were paid for by defendant Synthes. At the second surgeon training, defendant Synthes did not inform 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).

Only days later, a spine surgeon identified in the indictment as Doctor No. 6 told defendant Synthes 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 defendant Synthes was required to go to each institutional review board ("IRB") of each hospital participating in the "test market." Doctor No. 6 also told defendant Synthes 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." Doctor No. 6 also told defendant Synthes that, in his view, Synthes had risk management problems and needed more oversight of its clinical and compliance issues. The evidence would show that defendant WALSH was informed of Doctor No. 6's views, and also that defendant WALSH attended a meeting on September 23, 2003 following the death of Dr. No. 5's patient. The proof would also show that defendant WALSH attended a meeting on October 31, 2003 at which the death of Dr. No. 5's patient and additional findings from the University of Washington were both discussed. The outcome of these 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 evidence would show that at the end of October 2003, defendant WALSH advised another Synthes employee that in order for Synthes to obtain the FDA's permission to market Norian XR for the treatment of VCFs, Synthes would have to have the warning, "not intended for treatment of VCFs", removed, and that the only way this could be done was through a PMA application. See Exhibit C, attached.

In November 2003, while the Norian XR test market continued, defendant Synthes gave the four individual defendants an initial proposal for obtaining an IDE so that Synthes, like one of its competitors had recently done, might seek FDA permission to conduct clinical trials of its bone void filler in vertebroplasty surgeries for the treatment of VCFs ("the IDE proposal"), with the aim of getting the VCF warning bullet removed from the XR label. The evidence would show that defendant WALSH reviewed the IDE proposal before it was circulated. The IDE proposal was never shared with the FDA. After discussing the XR "test market" and the fact that two patient deaths had occurred as part of the "test market," the IDE

proposal discussed competitive activity with other products, stating that XR was the only product that the FDA required to add the warning bullet. "From 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." The IDE proposal went on to state:

> **Currently, Norian XR is being used off-label to treat VCFs.** The FDA has been very conservative regarding the treatment of VCFs and has issued numerous statements . . .cautioning companies . . . that the use of any material in vertebroplasty/kyphoplasty is off-label. The present state of the approved indication of Norian XR and the FDA bulletin puts Synthes in a compromising position. Synthes is at an increased legal risk with regards to product liability and medical malpractice . . . We recommend that Synthes pursue an IDE for the usage of Norian XR in treating VCFs. . . (Emphasis supplied).

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 notwithstanding 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. Also at the end of December 2003, Synthes released XR for limited sale beyond the original "test market."

On January 10 and 11, 2004, defendants Synthes and Norian 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]. The trial evidence would show that Doctor No. 4 re-worded the warning, which led to questions from the surgeons in attendance. The evidence would show that the company representatives did nothing to dispel any confusion that Doctor No. 4's

presentation may have caused. In addition, the XR Technique Guide went to all attendees, including the 30 surgeons.

On January 22, 2004, a spine surgeon identified in the indictment as Doctor No. 7 (who at the time was Doctor No. 6's partner) 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 ("the third death"). Doctor No. 7 could not rule out Norian XR as a cause of the third death. Once again, a sales consultant was present in the operating room during the surgery that resulted in the third death. Although defendants Synthes and Norian filed an MDR on the third death, that MDR was vague as to the surgery and its details. Moreover, defendants 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.

After the third death, defendants Synthes and Norian 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, defendants Synthes and Norian left XR on the market, and sent surgeons a misleading "dear surgeon" letter, which 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," while remaining silent about the warning bullet, and further omitted to state that:

-- Synthes had conducted a "test market" in which it had trained surgeons to use XR to treat VCFs;

-- the pilot studies indicated that Norian appeared to be a thrombogenic agent;[7] and

-- three patients had died on the operating table when spine surgeons had used Norian XR or its predecessor, SRS, off-label to treat VCFs.

The "dear surgeon" letter proves that defendant Synthes well understood the indication statement on the XR label, what it allowed and did not allow, and how narrow that indication statement really was.[8]

The United States respectfully submits that this summary of evidence provides a factual basis for the guilty plea by defendant JOHN J. WALSH to Count 97 of the indictment.

Respectfully submitted,

MICHAEL L. LEVY
United States Attorney

/s/ Mary E. Crawley
MARY E. CRAWLEY
GERALD B. SULLIVAN
DAVID J. CAPUTO
Assistant United States Attorney

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

[8] At trial, under Rule 404(b), Fed.R.Evid., the government would also introduce evidence that during and following an unannounced FDA inspection of defendants Norian and Synthes in May and June 2004, which inspection focused on the unauthorized SRS/XR unauthorized clinical trials, a number of individuals including defendant WALSH made false statements to the FDA investigator, and later to the FDA, on behalf of defendants Norian and Synthes.

EXHIBIT A

9/2008

IN THE UNITED STATES DISTRICT COURT

FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA	:	
v.	:	CRIMINAL NO. 09-
JOHN J. WALSH	:	

GUILTY PLEA AGREEMENT

Under Federal Rule of Criminal Procedure 11, the government, the defendant, and the defendant's counsel enter into the following guilty plea agreement. Any reference to the United States or the government in this agreement shall mean the Office of the United States Attorney for the Eastern District of Pennsylvania and the Office of Consumer Litigation of the United States Department of Justice.

1. The defendant agrees to plead guilty to Count One of an indictment or information, waiving prosecution by indictment, charging him under the "responsible corporate officer" doctrine with the strict liability misdemeanor offense of introduction into interstate commerce of medical devices that were adulterated pursuant to 21 U.S.C. § 351(f)(1)(B), and misbranded pursuant to 21 U.S.C. §§ 352(f), (o), in violation of 21 U.S.C. §§ 331(a) and 333(a)(1), all arising from Synthes's illegal test marketing and promotion of its medical devices Norian SRS and Norian XR in the United States between May 2002 and July 2004 and from the defendant's role as a corporate officer with responsibility to prevent such violations. The defendant further acknowledges his waiver of rights, as set forth in the attachment to this agreement.

2. This agreement is conditioned upon the following: (a) each of the defendant's individual codefendants, Michael D. Huggins ("Huggins"), Thomas B. Higgins ("Higgins") and Richard A. Bohner ("Bohner") (collectively, "the remaining individual defendants") entering a guilty plea in this case; and (b) acceptance of each of the guilty pleas of the remaining individual defendants by the United States District Court at the time of the guilty plea hearing. If the remaining individual defendants do not satisfy conditions 2(a) and 2(b), or if any of the remaining individual defendants subsequently seeks to withdraw his guilty plea, the United States, in its sole discretion, will be released from all of its obligations under this agreement. In addition, if any of the remaining individual defendants breaches his plea agreement, the United States, in its sole discretion, may void this defendant's plea agreement.

3. With regard to the Information to be filed pursuant to this agreement, defendant Walsh waives all defenses based on speedy trial under the Constitution or Speedy Trial Act, and any statutes of limitations. The defendant agrees that prosecution of the offense described in paragraph one above is timely as of the date that this agreement is signed and as of the date that the guilty plea will be entered in District Court. In the event that this agreement is not consummated, any party withdraws from it, or it is otherwise not fully carried out, including the following circumstances described in subparagraphs (a) through (h) of this paragraph, the defendant waives all defenses based on speedy trial and any statute of limitations with respect to the charge set forth in the Information to be filed pursuant to this agreement, for 90 days from the latest of any of these events: (a) Walsh's guilty plea is not accepted by the Court for any reason; (b) any of the remaining individual defendants's pleas is not accepted by the Court for any reason; (c) Walsh's conviction is later vacated for any reason; (d) any of the remaining individual

defendants's convictions is later vacated for any reason; (e) Walsh violates this agreement; (f) any of the remaining individual defendants violates his plea agreement; (g) Walsh's plea is later withdrawn; or (h) any of the remaining individual defendants's pleas is later withdrawn.

4. The defendant agrees to pay the special victims/witness assessment in the amount of $100 before the time of sentencing and shall provide a receipt from the Clerk to the government before sentencing as proof of this payment.

5. The defendant agrees to pay a fine of $100,000, and to make restitution in an amount to be determined by the Court at sentencing. The defendant further agrees that forfeiture, restitution, fine, assessment, tax, interest or other payments in this case do not constitute extraordinary acceptance of responsibility or provide any basis to seek a downward departure or variance from the applicable Sentencing Guidelines range.

6. Defendant waives any claim under the Hyde Amendment, 18 U.S.C. § 3006A (Statutory Note), for attorney's fees and other litigation expenses arising out of the investigation or prosecution of this matter.

7. At the time of sentencing, the government will:

a. Make whatever sentencing recommendation as to imprisonment, fines, forfeiture, restitution and other matters which the government deems appropriate.

b. Comment on the evidence and circumstances of the case; bring to the Court's attention all facts relevant to sentencing including evidence relating to dismissed counts, if any, and to the character and any criminal conduct of the defendant; address the Court

regarding the nature and seriousness of the offense; respond factually to questions raised by the Court; correct factual inaccuracies in the presentence report or sentencing record; and rebut any statement of facts made by or on behalf of the defendant at sentencing.

c. Nothing in this agreement shall limit the government in its comments in, and responses to, any post-sentencing matters.

8. The defendant understands, agrees and has had explained to him by counsel that the Court may impose the following statutory maximum sentence:

Count One: One year imprisonment, one year of supervised release, a $100,000 fine, and a special assessment of $25. Restitution and forfeiture may also be ordered.

The defendant further understands that supervised release may be revoked if its terms and conditions are violated. When supervised release is revoked, the original term of imprisonment may be increased by 1 year per count of conviction in the case of Class E felonies and misdemeanors. Thus, a violation of supervised release increases the possible period of incarceration and makes it possible that the defendant will have to serve the original sentence, plus a substantial additional period, without credit for time already spent on supervised release.

9. With respect to the conduct of Synthes, if the case had gone to trial, the United States would have proven the following, which is the basis for the plea, criminal fine and forfeiture:

a. The individual defendants, by virtue of their respective positions, were "responsible corporate officers" at various times during the events described below.

b. Synthes and its subsidiary, Norian marketed Norian SRS and Norian XR, each of which was a medical device within the meaning of 21 U.S.C. § 321(h)(1), and a significant risk device within the meaning of 21 C.F.R. § 812(m)(1).

c. Significant risk devices cannot be clinically tested without prior approval of the FDA, which approval is given through an investigational device exemption (IDE).

d. In the context of medical devices, clinical testing means research on one or more human subjects to determine the safety or effectiveness of the device.

e. Shipments of a medical device in interstate commerce must be accompanied by labeling bearing adequate directions for use for each of the medical device's intended uses. A manufacturer cannot market its device for a new intended use without notifying the FDA via a new 510(k) premarket notification. The failure to notify the FDA of a new intended use misbrands the device.

f. In December 2001, Norian SRS, a calcium phosphate compound, was cleared via the 510(k) process by the FDA as a bone void filler, to fill only those bony voids that were not intrinsic to the

stability of the bony structure, in the extremities, spine and pelvis. The Norian SRS label stated further that SRS was not to be mixed with any other substance. In December 2002, the successor device, Norian XR, which consisted of calcium phosphate with barium sulfate added for extra radiopacity, was cleared via the Special 510(k) process by the FDA, also as a bone void filler, with an indication statement identical to that of SRS. The Norian XR label further contained a warning: "not intended for the treatment of vertebral compression fractures."

g. Earlier, but no later than May 2002, Synthes and Norian learned that the FDA was concerned over the imprecision of the spine indication in the then-current indication for use of bone void fillers, and that the FDA understood that some surgeons, as part of their practice of medicine, were using bone void fillers in the spine for load bearing indications. The FDA asked that Synthes and Norian -- in their pre-market notification to the FDA seeking clearance of Norian XR -- provide additional labeling for Norian XR that specified that load-bearing indications, such as vertebroplasty, were not included in the product's indication for use. Defendants Synthes and Norian then promised the FDA that the companies would not promote Norian XR for vertebroplasty or other load-bearing indications without the appropriate regulatory authority.

The FDA continued to request such labeling until Synthes submitted the warning against vertebral compression fracture ("VCF") use that became a part of the Norian XR label.

h. Between August 2002 and December 2002, Synthes and Norian trained spine surgeons to mix Norian SRS with barium sulfate and to use the resulting medical device in vertebroplasty-type surgeries to treat VCFs, notwithstanding that the label of Norian SRS stated that the product was not to be mixed with any other substance. This training of surgeons to mix Norian SRS with barium sulfate for the treatment of VCFs violated 21 U.S.C. §§ 351(f)(1)(B), 352(o) and 352(f)(1) because the mixing made SRS a new device that required premarket approval or clearance for this new intended use, and that lacked adequate directions for such use.

i. Between August 2003 and January 2004, Synthes and Norian trained spine surgeons to use Norian XR in vertebroplasty-type surgeries to treat VCFs, notwithstanding that the label of Norian XR warned that the product was not intended for treatment of VCFs. This training took place as part of a so-called "test market" for Norian XR. As part of the XR "test market," Synthes and Norian directed the Synthes Spine sales force to gather clinical data about surgeries that the "test market" surgeons performed, so that Synthes and Norian could document the results of surgeries to treat

VCFs, in order to assess the risk level of using Norian XR to treat VCFs, and determine whether that risk level was too high. This unauthorized clinical testing of Norian XR for the treatment of VCFs violated 21 U.S.C. § 351(f)(1) because such testing of a significant risk device required the prior approval of the FDA, through an IDE.

j. Between December 2002 and January 2004, Synthes and Norian promoted Norian XR for use in vertebroplasty-type surgeries to treat VCFs, nothwithstanding that the label of Norian XR warned that the product was not intended for treatment of VCFs. The promotion of Norian XR for this additional intended use violated 21 U.S.C. § 351(f)(1), because Norian XR's labeling did not bear adequate directions for each of the device's intended uses, and in fact, warned against the intended use of treating VCFs.

10. The defendant may not withdraw his plea because the Court declines to follow any recommendation, motion or stipulation by the parties to this agreement. No one has promised or guaranteed to the defendant what sentence the Court will impose.

11. Pursuant to U.S.S.G. § 6B1.4, the parties enter into the following stipulations under the Sentencing Guidelines Manual effective November 1, 2008. It is understood and agreed that: (1) the parties are free to argue the applicability of any other provision of the Sentencing Guidelines, including offense conduct, offense characteristics, criminal history, adjustments and departures; (2) these stipulations are not binding upon either

the Probation Department or the Court; and (3) the Court may make factual and legal determinations that differ from these stipulations and that may result in an increase or decrease in the Sentencing Guidelines range and the sentence that may be imposed:

(a) The parties agree to disagree concerning whether U.S.S.G. §§ 2N2.1(a) or 2X5.2 applies in this case.

(b) The parties agree and stipulate that, as of the date of this agreement, the defendant has demonstrated acceptance of responsibility for his offense making the defendant eligible for a 2-level downward adjustment under U.S.S.G. § 3E1.1(a).

12. The defendant understands and agrees that in the event that this agreement is not consummated, any party withdraws from it, or it is otherwise not fully carried out, including the circumstances described in paragraph 3(a) through (h) above, defendant Walsh may thereafter be prosecuted for any criminal violation of which the United States has knowledge arising out of its investigation, notwithstanding the expiration of any applicable statute of limitations between the time when Walsh signed this plea agreement and the occurrence of any of the above events. In that event, Walsh (1) waives all defenses based on speedy trial under the Constitution or Speedy Trial Act, and any statutes of limitations, for 90 days from the latest of these events; and (2) agrees that he will not raise the expiration of any statute of limitations as a defense to any such prosecution, except to the extent that the statute of limitations would have been a defense pursuant to the terms of a Tolling Agreement between the parties effective December 17, 2008, all subsequent extensions of the Tolling Agreement, and this paragraph.

13. In exchange for the undertakings made by the government in entering this plea agreement, the defendant voluntarily and expressly waives all rights to appeal or collaterally attack the defendant's conviction, sentence, or any other matter relating to this prosecution, whether such a right to appeal or collateral attack arises under 18 U.S.C. § 3742, 28 U.S.C. § 1291, 28 U.S.C. § 2255, or any other provision of law. This waiver is not intended to bar the assertion of constitutional claims that the relevant case law holds cannot be waived.

a. Notwithstanding the waiver provision above, if the government appeals from the sentence, then the defendant may file a direct appeal of his sentence.

b. If the government does not appeal, then notwithstanding the waiver provision set forth in this paragraph, the defendant may file a direct appeal but may raise only claims that:

(1) the defendant's sentence on any count of conviction exceeds the statutory maximum for that count as set forth in paragraph 8 above;

(2) the sentencing judge erroneously departed upward pursuant to the Sentencing Guidelines;

(3) the sentencing judge, exercising the Court's discretion pursuant to United States v. Booker, 543 U.S. 220 (2005), imposed an unreasonable sentence above the final Sentencing Guideline range determined by the Court;

If the defendant does appeal pursuant to this paragraph, no issue may be presented by the defendant on appeal other than those described in this paragraph.

The defendant also waives all rights, whether asserted directly or by a representative, to request or receive from any department or agency of the United States any records pertaining to the investigation or prosecution of this case, including without limitation any records that may be sought under the Freedom of Information Act, 5 U.S.C. § 552, or the Privacy Act, 5 U.S.C. § 552a.

14. By entering this plea of guilty, the defendant also waives any and all rights the defendant may have, pursuant to 18 U.S.C. §3600, to require DNA testing of any physical evidence in the possession of the government. The defendant fully understands that, as a result of this waiver, any physical evidence in this case will not be preserved by the government and will therefore not be available for DNA testing in the future.

15. The defendant is satisfied with the legal representation provided by the defendant's lawyer; the defendant and this lawyer have fully discussed this plea agreement; and the defendant is agreeing to plead guilty because the defendant admits that he is guilty.

16. It is agreed that the parties' guilty plea agreement contains no additional promises, agreements or understandings other than those set forth in this written guilty plea agreement, and that no additional promises, agreements or understandings will be entered into unless in writing and signed by all parties.

SIGNATURES FOR THE UNITED STATES

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Assistant Attorney General
Civil Division
United States Department of Justice

EUGENE M. THIROLF
Director, Office of Consumer Litigation
United States Department of Justice

JOEL SCHWARTZ
Trial Attorney
Office of Consumer Litigation
United States Department of Justice

LAURIE MAGID
United States Attorney
Eastern District of Pennsylvania

LINDA DALE HOFFA
Chief, Criminal Division
Assistant United States Attorney

JOHN J. PEASE
Assistant United States Attorney
Chief, Health Care Fraud Section

MARY E. CRAWLEY
Assistant United States Attorney

GERALD B. SULLIVAN
Assistant United States Attorney

DAVID J. CAPUTO
Assistant United States Attorney

DATE: _____

SIGNATURE FOR JOHN J. WALSH

DATE: May 22, 2009

JOHN J. WALSH
Defendant

SIGNATURES OF JOHN J. WALSH'S ATTORNEYS

DATE: May 22, 2009

WILLIAM E. LAWLER, III
Vinson & Elkins, LLP
Counsel for Defendant

DATE: May 22, 2009

CRAIG D. MARGOLIS
Vinson & Elkins, LLP
Counsel for Defendant

Attachment

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

UNITED STATES OF AMERICA	:	
v.	:	CRIMINAL NO. 09-
JOHN J. WALSH	:	

ACKNOWLEDGMENT OF RIGHTS

I hereby acknowledge that I have certain rights that I will be giving up by pleading guilty.

1. I understand that I do not have to plead guilty.

2. I may plead not guilty and insist upon a trial.

3. At that trial, I understand

   a. that I would have the right to be tried by a jury that would be selected from the Eastern District of Pennsylvania and that along with my attorney, I would have the right to participate in the selection of that jury;

   b. that the jury could only convict me if all twelve jurors agreed that they were convinced of my guilt beyond a reasonable doubt;

   c. that the government would have the burden of proving my guilt beyond a reasonable doubt and that I would not have to prove anything;

   d. that I would be presumed innocent unless and until such time as the jury was convinced beyond a reasonable doubt that the government had proven that I was guilty;

   e. that I would have the right to be represented by a lawyer at this trial and at any appeal following the trial, and that if I could not afford to hire a lawyer, the court would appoint one for me free of charge;

   f. that through my lawyer I would have the right to confront and cross examine the witnesses against me;

   g. that I could testify in my own defense if I wanted to and I could subpoena witnesses to testify in my defense if I wanted to;

h. that I would not have to testify or otherwise present any defense if I did not want to and that if I did not present any evidence, the jury could not hold that against me.

4. I understand that if I plead guilty, there will be no trial and I would be giving up all of the rights listed above.

5. I understand that if I decide to enter a plea of guilty, the judge will ask me questions under oath and that if I lie in answering those questions, I could be prosecuted for the crime of perjury, that is, for lying under oath.

6. I understand that if I plead guilty, I have waived my right to appeal, except as set forth in appellate waiver provisions of my plea agreement.

7. Understanding that I have all these rights and that by pleading guilty I am giving them up, I still wish to plead guilty.

JOHN J. WALSH
Defendant

WILLIAM E. LAWLER, III
Counsel for the Defendant

CRAIG D. MARGOLIS
Counsel for the Defendant

EXHIBIT B

Gilbert, Jon - Dev Center

From: Gilbert, Jon - Dev Center
Sent: 10/17/2003 8:44:21 AM
To: 'lamongiere@erols.com' lamongiere@erols.com;
Cc:
Bcc:
Subject: FW: Question / concern

-----Original Message-----
From: Hamilton, Josi - Dev Center
Sent: Thursday, October 16, 2003 9:54 AM
To: Gilbert, Jon - Dev Center
Cc: Walsh, John - Dev Center
Subject: FW: Question / concern

-----Original Message-----
From: Hoffman, Vikki - Spine
Sent: Friday, February 28, 2003 1:01 PM
To: Hamilton, Josi - Dev Center; Weikel, Stuart - Spine
Cc: Sands, Barry - Spine; Gilbert, Jon - Spine
Subject: FW: Question / concern

Here is Nadine's response with regards to the literature that was passed out at AAOS. Josie, it is up to Barry whether we take her suggestions or not.

Thanks,

Vik
-----Original Message-----
From: Sloan, Nadine Y. [mailto:NYR@CDRH.FDA.GOV]
Sent: Friday, February 28, 2003 12:58 PM
To: 'HoffmanV@Synthes.com'
Subject: FW: Question / concern

Vikki,

Could you please let me know (by e-mail) when you receive this (so I know whether our e-mail has been corrected).

Thanks.

Nadine

-----Original Message-----
From: Sloan, Nadine Y.
Sent: Wednesday, February 26, 2003 5:38 PM
To: 'Hoffman, Vikki - Spine'
Subject: RE: Question / concern

Vikki,

Use 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 indications for the MQV bone void fillers require.

Assuming the labeling clearly represents a vertebral compression fracture, you may want to forward the apparently misbranded labeling to the appropriate persons in compliance. Although we (the division) do not deal with these issues directly, feel free to forward a copy to me for my information.

I hope this is helpful.

Nadine

-----Original Message-----
From: Hoffman, Vikki - Spine [mailto:HoffmanV@SYNTHES.com]
Sent: Tuesday, February 25, 2003 1:50 PM
To: Nadine Sloan (E-mail)
Cc: Sands, Barry - Spine
Subject: Question / concern

Nadine,

Several of our Engineers just returned from AAOS where some literature was being distributed for an inject able calcium phosphate for compression fractures. The literature clearly shows pictures of the spine with pedicle screws.

In order to receive clearance on our Norian XR, the FDA urged us to add the statement "Not intended for treatment of vertebral compression fractures" to the Warning section of out product insert. Am I to understand that as long as we clearly inform surgeons that Norian XR must be used with supplemental fixation (i.e., pedicle screws) we can indicate it for compression fractures in the spine?

Thank you for your consideration of this matter.

Vikki

Vikki M. Hoffman
Regulatory Affairs Project Manager
Synthes Spine
1380 Enterprise Drive
West Chester, PA 19380
610-647-9700 ext. 7563

EXHIBIT C

From: Walsh, John - Dev Center [DEVCENTER/CN=RECIPIENTS/CN=WALSHJ]
Sent: Tuesday, October 28, 2003 11:02 PM
To: Hamilton, Josi - Dev Center
Subject: RE: Indications for Norian XR

Josi,

Why can't we produce a DFU unique to the European market and leave the warning in question out? In order to get it removed in the U.S. will likely require a PMA. Let me know if you still want me to follow-up with the FDA.

Thanks,

John

-----Original Message-----
From: Hamilton, Josi - Dev Center
Sent: Tuesday, October 28, 2003 11:09 AM
To: Walsh, John - Dev Center
Subject: FW: Indications for Norian XR

John –

Can we talk to the FDA to find out what we need to do to get that bullet removed?

-----Original Message-----
From: Anne-Catherine.Ferber@stratec.com [mailto:Anne-Catherine.Ferber@stratec.com]
Sent: Tuesday, October 28, 2003 11:01 AM
To: Sabine.Gass@stratec.com; Cynthia_Hitchcock@norian.com; HamiltoJ@synthes.com
Cc: GeskesK@synthes.com; Marianne.Buergi@STRATEC.com; Manuel.Schaer@STRATEC.com; RichardsonD@synthes.com
Subject: AW: Indications for Norian XR

Dear Sabine,

The situation with the Norian XR DFU (see first attachment) is the following:
<< File: 20-1017-A .pdf >>
1) When Synthes has submitted the Norian XR premarket notification to the FDA, there were no comment in the original DFU under point "warning" against vertebral compression fractures. So apparently, from the Product Development side there is no clinical reason not to use Norian XR in vertebral compression fractures. Josi, please correct if I'm wrong.
Finally it was a request from the FDA that Synthes should specifie that "load bearing indications, such as vertebroplasty, are not included in the current indication for use". This decision of the FDA was apparently motivated by the fact they don't want to take a position towards vertebroplasty. But the situation may be different in Europe, as there are already some cements CE marked for vertebroplasty (e.g Cortoss from Orthovita, Vertebroplastic from Depuy, KyphX from Kyphon...).

2) Concerning the comment of Cynthia, the DFU for Norian SRS do not include the statement "not intended for treatment of vertebral compression fractrures, see point "Warning" of the following attachment.

<< File: Pouch DFU - outside pages.pdf >>
Can you please clarify this very important issue with very high priority, otherwise it would not be possible to promote Norian XR as the main indication in Europe will be vertebroplasty.

Kind regards

Catherine

-----Ursprüngliche Nachricht-----
Von: Cynthia_Hitchcock@norian.com [mailto:Cynthia_Hitchcock@norian.com]
Gesendet: Montag, 27. Oktober 2003 16:07
An: Anne-Catherine.Ferber@stratec.com; GeskesK@synthes.com
Cc: Marianne.Buergi@STRATEC.com; Manuel.Schaer@STRATEC.com; HamiltoJ@synthes.com; RichardsonD@synthes.com
Betreff: RE: Indications for Norian XR
Wichtigkeit: Hoch

This decision has to come from the Product Development team and Corporate Legal. However, my position is that the DFU should continue to state the original contents, which includes the statement. Also cross reference the SRS DFU and if that DFU still includes the statement, then there should be NO change in the XR DFU.

Cynthia

-----Original Message-----
From: Anne-Catherine.Ferber@stratec.com [mailto:Anne-Catherine.Ferber@stratec.com]
Sent: Friday, October 24, 2003 7:14 AM
To: Cynthia_Hitchcock@norian.com
Cc: Marianne.Buergi@STRATEC.com; Manuel.Schaer@STRATEC.com; HamiltoJ@synthes.com; RichardsonD@synthes.com
Subject: Indications for Norian XR

Dear Cynthia,

I'm working on the translation of the DFU booklet for Norian XR.

I have seen that in the chapter 3 "Warnings" that Norian XR is not intended for treatment of vertebral compression fractures.
I know that in the States the FDA apparently won't give approval for any cements for vertebral body augmentation, but do we really have to note this in the European DFU? The situation is different here as a couple of cement already received the CE mark for vertebroplasty (Cortoss from Orthovita, Vertebroplastic from Depuy, KyphX from Kyphon...).

Looking forwards for your answer.
Best regards

Catherine Ferber
Product Manager Spine

STRATEC Medical
CH-4436 Oberdorf
Tel +41 61 965 65 57
Fax +41 61 965 66 16
anne-catherine.ferber@stratec.com

CERTIFICATE OF SERVICE

I hereby certify that I have caused to be served a true and correct copy of the annexed Guilty Plea Memorandum on counsel for the defendant **JOHN J. WALSH**, by electronic filing:

William E. Lawler, III, Esq.
Craig D. Margolis, Esq.
Vinson & Elkins LLP
The Willard Office Building
1455 Pennsylvania Avenue NW
Suite 600
Washington, DC 20004-1008

/s/ Mary E. Crawley
MARY E. CRAWLEY
Assistant United States Attorney

DATE: July 17, 2009