

Establishment Inspection Report

Depuy Orthopaedics, Inc.
Warsaw, IN 46582-3994

FEI: **1818910**
EI Start: 01/28/2008
EI End: 01/28/2008

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SUMMARY

This Bioresearch sponsor inspection was assigned as a PMA Based High Priority Directed Inspection assignment from the Division of Bioresearch Monitoring, HFZ-312 Center for Devices and Radiological Health under FACTS #882693. This MDUFMA based assignment requested limited focus on the integrity of study data for PMA (b) (4) IDE (b) (4) "A Clinical Study of the (b) (4)" The inspection was also conducted as part of the DET-DO (FY 2008) work plan assignments in accordance with Compliance Program 7348.810- Sponsors, Contract Research, Organizations and Monitors.

There is no previous record of this firm being inspected as a Sponsor. However, the firm was inspected as a Medical Device Manufacturer, most recently on 12/3, 4, 5, 6/2007 and 1/22/08. The scope of the inspection involved Post Market Surveillance and Recall Activities for eight (8) product recalls listed in FDA's Recall Enterprise System Database. An FDA-483 Inspectional Observations List was issued for a design flaw that involved the Acclaim Total Elbow System. The inspection was classified as VAI.

A Post Market Audit inspection was also performed on 10/16, 17, 18/07, which covered the Duraloc Options Acetabular Cup System device for hip replacement or modular hip endoprosthesis; this inspection was classified NAI.

The current inspection was limited in focus on the integrity of study data as it relates to the Clinical Study of the (b) (4), PMA

(b) (4) At the close of the inspection, various issues were discussed with management; such as:

- The criteria used to terminate Clinical Investigator sites that fluctuate in and out of compliance may need re-evaluation. For example, even though compliance was secured after corrective actions were put into place at site #01, on several occasions, there were new issues that arose during each monitoring visit. However, based on the firms SOP, the site was not eligible for termination since the issues did not fall into any of the categories' outlined in the written procedures.
- Although there were work instructions (SOPs) for the general monitoring of clinical investigator sites, there was no specific monitoring plan for the (b) (4) (b) (4) study until approximately one year after the study was initiated.
- There were instances where clinical investigator sites reported (anticipated) adverse events weeks and sometimes months after the events occurred. Although, the protocol

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does not require timeframes for the reporting of anticipated adverse events, discussion was held regarding the assurance that each CI site is appropriately identifying adverse events for reporting purposes.

- There were sometimes difficulties in ascertaining the disposition of study devices after shipment. Even though the system provides the dates shipped and returned, the devices are initially shipped to a distribution site which is subsequently provided to the clinical investigator by a DePuy representative; the records do not easily reflect this system.

At the close of the inspection, management provided a revised work instruction regarding the termination of clinical investigator sites.

Additional issues were confirmed during this inspection such as:

- No data integrity issues were noted.
- With regard to the (b) (4) data for various subjects were not submitted to the agency due to the fact that some subjects did not meet the criteria for the US study; such as: (b) (4) (b) (4) As a result, subjects with these exclusionary identifiers for the US protocol were not submitted to the agency. The missing data was provided during the inspection.

ADMINISTRATIVE DATA

Inspected firm: Depuy Orthopaedics, Inc.
Location: 700 Orthopaedic Dr
Warsaw, IN 46582-3994
Phone: 574-372-7340
FAX:
Mailing address: 700 Orthopaedic Dr
Warsaw, IN 46582-3994

Dates of inspection: 1/28,29,31,2/4,5,8,11/08
Days in the facility: 7
Participants: Myra K. Casey, Investigator

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Note: This report may contain CONFIDENTIAL information, exhibits and attachments that contain patient/subject identifier information such as names, identification numbers and medical information.

HISTORY

DePuy was founded in 1895 in Warsaw, IN as a manufacturer of orthopedic products. During the late 1980's, the firm expanded its operation into Europe which subsequently resulted in the purchase of Chevalier in Switzerland. Other operations were acquired such as the CF Thackray in Leeds, UK. Since the 1990's this location was known as DePuy International Headquarters.

The corporation currently designs, manufactures and distributes orthopaedic devices and supplies such as hip and knee products.

During November 1998, DePuy was acquired by Johnson and Johnson (J&J) company whose corporate offices are located at One Johnson & Johnson Plaza New Brunswick, New Jersey 80933.

The Warsaw, IN facility is housed on a (b) (4). The operation has (b) (4) employees with (b) (4) in the Clinical and Regulatory Affairs Department and (b) (4) in Quality and Compliance.

International products are manufactured, warehoused and distributed from this site. Other operations include, purchasing, supplier quality, receiving inspection and contract manufactured products and raw materials.

DePuy also maintains two additional U.S. sites that manufacture and or store products; they are:

- Raynham, MA-This site manufactures DePuy Orthopaedics and Depuy International products. Also, purchasing, supplier quality inspection and contact manufacturing of products and raw materials are handled at this site.
- Bridgewater, MA-This site is responsible for the inspection of DePuy Orthopaedics raw materials, components and finished products.

(Exhibits #1, #2)

DePuy began activities as a Sponsor of Clinical Research studies after 1976. The first Pre-Market Approval (PMA) product, which was approved in 1983, was the "Porous Coated AML Hip Stem" for general use as a biologically fixed implant. The firm subsequently received an initial PMA

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approval for the LCS Total Knee System and different components of this system in 1992 and 1994. (Exhibits #1 & #2)

The firm currently markets the DePuy (b) (4) which consists of a (b) (4) (Exhibit #2)

The following clinical sites were enrolled into the study as part of investigational and control groups:

Investigational Sites-

- (b) (4) -US (b) (4) enrolled, 1 withdrawal)
- (b) (4) (b) (4) enrolled, 0 withdrawals)
- (b) (4) Canada (b) (4) enrolled, 1 withdrawal)
- (b) (4) Canada (this site was subsequently converted to a control site) (b) (4) enrolled, 1 withdrawal as an investigational site, (b) (4) enrolled as a control site with 0 withdrawals)
- (b) (4) -UK (b) (4) enrolled, 1 withdrawal)
- (b) (4) UK (b) (4) enrolled, 3 withdrawals)

Control Sites-

- (b) (4) -US (b) (4) enrolled, 0 withdrawals)
- (b) (4) -US (b) (4) enrolled, 1 withdrawal)
- (b) (4) M.D-US (b) (4) enrolled, 2 withdrawals)

(b) (4)
(Exhibit #3)

(b) (4) was pending approval; however was not included in the study due extended time frames for obtaining IRB approval.

During (b) (4) DePuy received clearance to market the (b) (4)
(b) (4)

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The (b) (4)
(b) (4)
(b) (4)

(b) (4)

The enrollment dates for the (b) (4) Study is August 2004 through November 2006.

Any agency correspondence should be forwarded to following person:

William Weldon, Chief Executive Officer
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933

INTERSTATE COMMERCE

The (b) (4) Hip Prosthesis System IDE (b) (4) is manufactured by DePuy International Ltd, St. Anthony Road Beeston Leeds LS11 8DT England. The (b) (4) study devices are stored and distributed from the Warsaw, IN site. Most of the study articles are shipped through interstate commerce.

Listed are the clinical investigators and study sites:

(b) (4)

(b) (4)

Exhibits #5-#7 are copies of label specifications and labeling information for the Standard Acetabular Cup and Femoral Resurfacing Heads Head.

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JURISDICTION

DePuy designs, manufactures and distributes various orthopaedic devices and supplies (i.e. hip, knee) and operating room products. (Internet source from website @www.depuyorthopaedics.com)

(b) (4)

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

On 1/21 & 22/08, I initiated pre-inspection contact with **(b) (6)** (firms' contact) by telephone and left a message. On 1/23/08, I spoke to **(b) (6)** who stated that she would determine which day would be the best to initiate the inspection, based on the availability of all persons involved. We agreed that the inspection would begin on the following Monday on 1/28/08.

On 1/24/08, I spoke to **(b) (6)** by telephone and requested that various information and records be available for review during the inspection such as: a list of Non-Significant Risk Devices (NSR); Humanitarian Use Devices (HUD); Organizational Chart; Outside Services and Contractor (CRO's, IRB's); and Clinical Investigator signed agreements.

On 1/28/08, I displayed my credentials and issued an FDA 482-Notice of Inspection to Ms. Pamela L. Plouhar, Vice President, Clinical and Regulatory Affairs. Ms. Plouhar acknowledged that she was the most responsible person in charge of the Clinical Research operations. Ms. Plouhar stated that she oversees the operations of the Clinical and Regulatory Programs.

The following individuals were also present during the initial meeting: Ms. Dee Furr, Manager Clinical Research Staff-Warsaw & Miami; Ms. Vesna Zovkic Manager, Clinical Research; Mr. James "Jim" Sheets, Manager, Clinical Quality Warsaw; Ms. Kimberly Dwyer, Clinical Research Project Leader; Ms. Keli Hankee (formerly Wakeland), Senior Clinical Research Associate; Ms. Laura J. Fazio, Team Leader, Clinical Data Management; and Ms. Beth Becotte, Clinical Quality Manager (based in Raynham, MA).

During most of the inspection, various individuals provided me with information and records; they are as follows: Ms. Pamela Plouhar; Ms. Keli Hankee; Ms. Kimberly Dwyer; Mr. James Sheets; Ms. Laura J. Fazio; and Ms. Beth Becotte (present during the first two days of the inspection).

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I was also provided with information and/or records throughout the inspection by the following individuals: Ms. Kathy Harris, Director, Regulatory Affairs; Mr. Michael Rhee, Product Director, Hip Marketing; Mr. Paul M. Berman, Group Product Director, Hip Marketing; Ms. Niki Seibert, Manager Clinical Technical Systems; Ms. Deborah Silor, Worldwide Manager, Computer System Validation (CSV) & Compliance; Ms. Keli McLeod, Project, Manager, CSV/Compliance; and Mr. Paul Voorhorst, Director, Biostatistics & Data Management.

During the initial meeting, various individuals provided a presentation on the history of the firm, the vision, mission and quality policy and a summary of the DePuy (b) (4) study. In addition, information was provided regarding the firms' organizational structure and specific roles relating to the Clinical Research Program. (Exhibit #9)

At the close of the inspection, various issues were discussed with the following individuals: Ms. Pamela Plouhar; Ms. Dee Furr; Ms. Vesna Zovkic; Ms. Keli Hankee; Ms. Kimberly Dwyer; Mr. James Sheets; and Ms. Laura J. Fazio.

ORGANIZATION AND PERSONNEL

The overall organization of the clinical research and monitoring activities involves various departments; such as: Clinical Research and Regulatory Affairs and Biostatistics and Data Entry. (Exhibit #2, #9)

Ms. Plouhar oversees the Clinical Research Department and maintains direct responsibility for (b) (4) study; she maintains oversight for the following operations: protocol development, selection of investigators, monitoring, compliance, FDA submissions, adverse events and device accountability.

Ms. Keli Hankee, Senior Research Associate stated that she was responsible for the following, as it relates to the (b) (4) clinical study: protocol development; conducting on-site visits; assuring IRB approvals; informed consents; case report forms; enrollment; adverse experiences, final evaluations and decisions; selection of clinical investigators (in addition to a team of persons in the Clinical Research Department); oversee monitoring of sites (time frames and compliance follow-up); and preparing clinical portions of the PMA.

DePuy maintains a Clinical Quality Assurance (CQA) unit that is "responsible for the conduct of routine GCP compliance audits of clinical investigators involved in clinical trials", per the written work instructions "WI-3832." (Exhibit #2)

Mr. James "Jim" Sheets stated that some of his duties as the Clinical Quality Manager are to perform auditing functions for clinical investigational sites; data base operations; and Contract Research Organizations (CRO). Mr. Sheets started with DePuy during 3/07. (Exhibit #10-SOP for QA Audits)

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Outside Contractors

Various outside services and contractors (current and former) were used for the (b) (4) clinical study; these services are written in agreements and were submitted to the agency.

Listed are some of these outside contractors used for the (b) (4) clinical study:

(b) (4)

(b) (4)

(b) (4)

(CRO) for US sites & Monitoring

(b) (4)

(b) (4)

Analysis Reviewer

(b) (4)

(b) (4)

Consultant

(b) (4)

Clinical Research Associate

(*See Exhibits #11-#18 for contractual agreements, curriculum vitae's, and training)

IRB's

Records indicate that each clinical investigator site received Institutional Review Board (IRB) approval prior to enrollment of subjects. (Exhibit #19)

Listed are the study sites and approving IRB's:

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Control Site Investigator-US	IRB Name, Chairman	IRB Approval Date
(b) (4)	(b) (4)	2/9/05
(b) (4)	(b) (4)	7/8/04
	(b) (4)	11/11/05
(b) (4)	(b) (4)	8/17/04
(b) (4)	(b) (4)	5/13/04
	(b) (4)	8/11/05
(b) (4)	(b) (4)	10/13/04
(b) (4)	(b) (4)	12/13/06
(b) (4)	(b) (4)	12/16/04

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(b) (4)	
(b) (4)	12/16/04
(b) (4)	12/16/04

Exhibits #20-#23 are charts of Clinical Investigator and IRB approvals for 2005, 2006, and 2007.

Exhibits #24-30 are copies of original IRB approvals, continuing reviews, amendment reviews, and site withdrawals.

SELECTION AND MONITORING OF CLINICAL INVESTIGATOR

The selection of Clinical Investigators (CI) is conducted in accordance with work instruction (WI-0741) "Investigator Nomination and Selection." This procedure outlines various levels of the selection process; such as: submission of nominations; classification of nominees into Tiers/groups based on qualifications; verification of licenses; Clinical Compliance Specialist (develops consulting agreement); and final selection of CI.

The nominee must meet the minimum professional requirements, maintain adequate experience with the device and surgical technique (or similar device and procedure), and maintain appropriate resources to perform the clinical study. (Exhibit # 31-electronic copy of SOPs on CD as #WI 0741 with corresponding Table of Contents)

Ms. Keli Hankee, Study Manager stated that a team agrees on the criteria for selecting clinical investigators for a particular study (i.e. Marketing, Research & Development and Clinical Research).

I reviewed records which showed that each Clinical Investigator involved in the (b) (4) Clinical Study IDE (b) (4) initially obtained written information regarding the study. Furthermore, each CI received a Pre-Investigational Visit (PIV) from the sponsor prior to enrollment. Exhibit #32 is a copy of monitoring visit dates.

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Exhibits #33-#39 are copies of notifications (by letter) to clinical investigators regarding the Pre-Investigational Visit and literature regarding the ASR study.

During visits, the monitor completes a “Pre-Investigational Site Visit Report or a “Monitoring Site Visit Report” that assures that various areas of the study is being covered such as: discussion of protocol; adequate and accurate record keeping (discussion and explanation of format of Case Report Forms (CRF’s) and informed consents); accurate records of inventory control; and discussion of the regulatory binder. **(Exhibit #40-#42)**

The sponsor did not terminate any clinical investigators from participating in the (b) (4) IDE (b) (4) study.

In addition, DePuy maintains internal and external monitors to oversee clinical studies. **(Exhibit #9)** The Clinical Research staff including the monitor’s are provided with training which is outlined in a training matrix. For example, the Regional Monitor participated in training such as: Clinical Investigator’s Regulatory Binder; Noncompliance and Termination of a Clinical Investigator; Data Collection and Handling; and Evaluation and Reporting Adverse Events for Regulated Clinical Investigations. **(Exhibit #43)**

MONITORING PROCEDURES AND ACTIVITIES

The sponsors’ monitoring procedures are outlined in work instruction WI-0427. As indicated, “The procedure defines the objectives, frequency and required processes for visiting sites participating in clinical investigations sponsored by DePuy Orthopaedics.” **(Exhibit #44)**

Initially, the firm’s work instructions (WI-0427) indicated that a site should be monitored every (b) (4) months at a minimum; however, it was revised to monitor the sites every (b) (4) months during enrollment and subsequently every (b) (4) months. **(Exhibits #44-SOP Revision A, Exhibit #45 Revision B)**

During the initial monitoring of a site, various areas contained in the Pre-Investigation Site Visit Report and subsequently the Monitoring Site Visit Report (formerly the Periodic Monitoring Site Visit Report) are covered; such as: number of enrollees, persons present during visit, discussion of protocol with CI, operative technique per protocol, discussion of investigation plan, record keeping (informed consent forms, CRF’s and source documents), accurate records of inventory control (location of investigational devices), monitoring obligations and visits, site inspection of facilities (operating room, medical records), and investigator qualifications (investigator’s agreement, IRB approvals).

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The report also maintains a narrative section that summarizes issues, discussions during the visit including protocol violations. Compliance issues are tracked and documented in this report including the person responsible for the follow-up and dates of resolution by the sponsor or monitor if corrective action was done during the visit. **(Exhibits #46-55)**

Although the required evaluation of a monitoring site is (b) (4) Ms. Hankee stated that usually about (b) (4) of records and operations are audited during site visits.

Discussion was held with management at the close of the inspection regarding the lack of a monitoring plan for the (b) (4) study, which was not implemented until approximately one (1) year after the beginning of the study. **(Exhibit #56)**

REVIEW OF SUBJECT RECORDS

I reviewed at random selected Case Report Forms (CRF) that were prepared and submitted by the study sites. DePuy does not maintain any source documents; they are stored at each investigational site. The firm's procedure (WI-0427) indicates that the monitor conducts some of the following tasks upon review of records at investigational sites:

- Compare source documents (e.g. medical charts, clinical charts) to site CRF's and subject data sheets.
- Review and reconcile data and study supplies.
- Review regulatory documents/Investigators Binder to assess compliance with FDA, IRB and Sponsor requirements (per WI-0359).
- Verify adequacy of facility and staff.
- Confirm appropriate storage, recording and utilization of controlled investigational devices.
- Complete applicable columns of Inventory Reconciliation Worksheet.
- Review corrective actions.
- Provide on-site training to address deficiencies identified prior to or during monitoring visit.

I reviewed IRB approvals and verified that the CI sites received approval prior to enrollment of subjects. **(Exhibits #19 & #57)**

Additionally, I reviewed Monitoring Site Visit Reports to ascertain whether informed consents were signed prior to enrollment. The firm submitted a letter dated 6/30/05 to the agency regarding an incident where subject (b) (6) received the study device prior to the subject signing the

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informed consent. The letter indicates that the patient and Clinical Investigator discussed the study and investigational device in length prior to implantation. **Exhibit #58**

Deviations and adverse events are documented on the cover page of Monitoring Site Visit Reports (i.e. adverse events, protocol violations, or voluntary withdrawals). Each section of the report provides for comments where deviations may have occurred (i.e. Patient Review, CRF Review, Investigational Devices).

Furthermore, there is a section in the report for documenting protocol violations/deviations, action plans, items pending from the previous monitoring visit, narrative and action to be taken by the site, and action to be taken by the monitor. The completion dates for these items are also indicated.

Addendum items (of actions taken) are also recorded on these reports. For example, various subjects were evaluated for the clinical study more than 14 days prior to surgery, which is a protocol violation. The agency and IRB were alerted to this issue. **(Exhibits #52, #59-#62)**

I did not note any issues that were not acknowledged and/or addressed by the sponsor.

TEST ARTICLE

The DePuy (b) (4) is a multi-center, prospective, unblinded, non-randomized, concurrently controlled clinical trial of the DePuy (b) (4)

(b) (4)

(b) (4) (Exhibit #4)

(b) (4)

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RECORD RETENTION

Case Report Forms (CRF's) are maintained in secured file cabinets by the sponsor in the Clinical Research Department. CRF's are also maintained electronically. However, source documents are not maintained by the sponsor; they are verified and reviewed during visits at clinical investigator sites. (Exhibit #32-procedure (b) (4) for the retention of electronic files)

CDRH ASSIGNMENT REQUEST

This PMA-based High Priority Directed inspection was assigned from the Division of Bioresearch Monitoring, HFZ-312, and Center for Devices and Radiological Health (attached); the following issues were covered in response to this assignment:

Each Clinical Investigator involved in the (b) (4) IDE study signed an Investigator Agreement, in addition to co-investigators, in some cases.

Site #	Clinical Investigator	Investigator Agreement Date
(b) (4)	(b) (4)	6/30/04
		7/27/04
		7/19/04
		7/30/04
		7/16/04
		8/20/04
		1/20/05
		10/6/04
		9/29/04

(*Exhibit #63-#65)

Records indicate that each CI and their staff received training which consisted of meetings, teleconferences, web training and on-site training; for example:

- Initial training was provided on 9/22/03 in (b) (4) to clinical investigators; some of the following items were covered: Investigator's Responsibilities; Statistical Analysis; Protocol

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Review: Case Report Form Review; and Radiographic Protocol. Drs. (b) (4) (b) (4) were present during this meeting. (Exhibit #66)

- On 12/8/04, a meeting was held in (b) (4) for Clinical Investigator's. One physician participated by teleconference. This meeting covered IDE/PMA regulatory issues, radiographic protocol techniques, and surgical techniques. A handout of information was provided to the participants. (Exhibit #67)
- A videoconference presentation was provided on 12/18/03 that covered issues; such as: study purpose and objectives; subject eligibility; informed consent; subject management; and surgical techniques. (Exhibit #68)
- On 9/28/05, a Clinical Investigator Meeting was held in (b) (4). The agenda included clinical data summaries, radiographic data summaries, and adverse event reporting. (Exhibit # 69)
- On 6/6/07 an (b) (4) Investigator Meeting was held. Most of the investigator's involved in the (b) (4) study were present. The meeting covered issues such as; clinical data, contents of the PMA, proposed indications, compliance issues; and safety and efficacy. (Exhibit #70)

In addition, CI's and training coordinators were provided with training regarding the (b) (4) study prior to enrollment of subjects.

Records indicate that Regulatory Binders, inventory control and a synopsis of the (b) (4) study was reviewed during each initial visit. Monitoring reports also show that training occurred on-site during monitoring visits. (Exhibits #33-#39)

Deviations from the protocol or regulations that occur at Clinical Investigator sites are documented in Monitoring Site Visit Reports and followed-up by the sponsor. A narrative of the issues are described in detail and listed in the protocol deviation section of the report.

In some instances, corrective action may occur on-site and handled immediately by retraining or discussion. Other situations may involve additional correspondence and follow-up after the visit. For example, the Monitoring Visit Report for site #01 indicates that there were unreported adverse events for various subjects (i.e. (b) (6)). The required follow-up indicates the person responsible for resolving this issue and due date. The sponsor confirmed the issue by initialing and dating the report. (Exhibit #71)

Ms. Hankee showed me additional examples of compliance issues that were identified and subsequently resolved. (Exhibits #51-#55, #71-73)

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Ms. Hankee stated that she is responsible for the tracking and closure of deviations found at the study sites.

Upon review of violations in Monitoring Site Visit Reports and CRF's, various serious violations were reported to the agency via letter. **Exhibits #74**

Although, no investigators were terminated from participating in the (b) (4) IDE (b) (4) study, upon review of Monitoring Site Visit Reports for site #01 (b) (4) I noted various instances of non-compliance (which were subsequently corrected). However, I discussed with management whether the site had ever been considered for termination due to the amount of issues found during each visit.

According to Ms. Plouhar, they were aware that several compliance issues were identified at site #01; however, none of them "rose to the level" of termination. She further pointed out that the work instruction #W1-0363 entitled, "For-Cause Termination of a Clinical Investigator/Investigational Site" outlines certain criteria for terminating a Clinical Investigator, but none of the issues fell into any of these categories; for example:

- Repeated failure to obtain properly executed Informed Patient Consents;
- Failure to maintain adequate control of the study devices;
- Repeated or intentional failure to report serious device related adverse effects;
- Persistent use of the study device outside of the study protocol without obtaining prior approvals; from the sponsor, FDA and the IRB;
- Failure to report to the sponsor the withdrawal of the IRB's approval for the study;
- Falsification of the investigations records and/or date reported to the sponsor;
- Fraudulent activities with respect to the sale of the investigational device;

The procedure also indicates that either compliance will be secured promptly or the investigator's participation will be terminated per 21 CFR 812.46. (**Exhibit #75**)

Ms. Plouhar also explained that each site must maintain an (b) (4) or above compliance rate with regard to the deviations found during the monitoring visits. This compliance rate is monitored for each CI to assure that an acceptable percentage is being maintained. **Exhibit #76**

She further explained that DePuy is very serious about Clinical Investigator compliance and pointed out that due to the issues being identified at site #01, she personally visited the site, along with the Regional Monitor on 6/8/05. They met with the Clinical Investigator and the Study Coordinator and discussed the previous monitoring visit conducted on 5/12, 13/05, which involved the telephoning of subjects for their (b) (4) interval visit instead of visiting the office (which is required by the

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protocol). **(Exhibit #77)** This issue was reported to the agency and the IRB and the process was subsequently waived. **(Exhibit #78 & 79)**

In addition, I was provided telephone and e-mail correspondence between DePuy and site #01 regarding the follow-up of various compliance issues; such as: missing subject self assessments for 2 patients; findings on a **(b) (4)** radiograph for a patient; withdrawal of patient **(b) (6)** and site #01 compliance rate. **(Exhibits #80-85)**

At the close of the inspection, Ms. Plouhar showed me a revised (draft) Work Instruction procedure which provides additional details regarding the termination of an Investigational site and its involvement in a study due to non-compliance.

I verified that there are no discrepancies between the assignment and firm's information involving IRB information (approvals etc.) and participating Clinical Investigators. No discrepancies were noted. **(Exhibits #19-#28)**

I also reviewed and verified records involving IRB approval dates for the **(b) (4)** study at each site. **(Exhibit #19, 24-28)** No deficiencies were noted.

Monitoring procedures are outlined in work instruction WI-0427. As indicated, "The procedure defines the objectives, frequency and required processes for visiting sites participating in clinical investigations sponsored by DePuy Orthopaedics, for the purpose of conducting routine business related to the clinical investigation." **(Exhibit#44, #45)**

The monitoring procedures also outline the issues covered during Pre-Investigation Site Visits, which are recorded on a "Monitors Pre-Investigational Site Visit Report." This report indicates general information; such as: number of enrollees; persons present during visit; discussion of protocol with CI; operative technique per protocol; discussion of investigation plan; record keeping (informed consent forms, CRF's and source documents); accurate records of inventory control (location of investigations devices); monitoring obligations and visits; site inspection of facilities (operating room, medical records); and investigator qualifications (investigator's agreement, IRB approvals). In addition, this site visit report provided for a narrative description of issues that were discussed and/or noted during the site visit.

Furthermore, the Work Instruction maintains a Site Visit Overview Table which summarizes each are to monitor during each visit (pre-investigational, interim visit, etc.)

Although the required evaluation of a monitoring site is **(b) (4)** Ms. Hankee stated that usually about **(b) (4)** of records and operations are checked during site visits.

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I was also provided with the site visits for the Pre-Investigational (PIV) and Interim Monitoring Visits (IMV) for each study site; for example:

CI	Visit Type	Visit Date
(b) (4)	PIV	07/29/04
(b) (4)	IMV	02/10/05
(b) (4)	IMV	05/12, 13/05
(b) (4)	IMV	07/21, 22/05
(b) (4)	IMV	09/26, 27/05
(b) (4)	IMV	02/13, 14/06
(b) (4)	IMV	10/16, 17/06
(b) (4)	IMV	02/08, 9/07
(b) (4)	IMV	05/30, 31/07
(b) (4)	IMV	11/28, 29/07

The firm's work instruction (WI-0427) initially requires investigational sites to be monitored every (b) (4) months at a minimum; however, Ms. Hankee stated that they are usually performed more frequently. (Exhibit #32 for CI visit dates)

The work instructions were revised (dated 8/30/05) to conduct on-site visits at intervals not to exceed (b) (4) months during patient enrollment, and (b) (4) months during the patient follow-up phase. (Exhibit #45)

Discussion was held with management at the close of the inspection regarding the lack of a specific Monitoring Plan for the (b) (4) study, which was not implemented until 8/30/05, approximately 1 year after the study was initiated. (Exhibit #56)

Management acknowledged that a monitoring plan for the (b) (4) study should have been implemented prior to this time period.

As previously indicated in item #2, compliance issues are documented and tracked (i.e. Protocol Non-Compliance) and Monitoring Site Visit Reports. Issues are followed-up either on-site, by correspondence (letter or telephone) or visit. Exhibits #51-#55, 71, 73 and 74

The computer system is hosted by (b) (4), which utilizes (b) (4). The (b) (4) clinical study is maintained in the (b) (4)

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Each clinical study site records data manually in Case Report Forms (CRF's) and sent to the sponsor. Upon receipt, the sponsor enters the data into the computer system using the "dual pass" system. This procedure involves two individuals entering the same information and a third person verifying/comparing the entries.

If discrepancies, omissions or additional information is identified between CRF's and computer data, a Data Issue Form (DIF) will be generated. **(Exhibit #86)** These forms are sent to the site for clarification/corrections.

Protocol deviations and violations are also tracked in the computer system. These deviations are initially recorded on a "Protocol Deviation/Violation report/form. **(Exhibit #87-WI 2963)**

Data base quality control (QC) is performed on a yearly basis. Critical data points in the CRF are checked against the database data for accuracy. **(Exhibit #31-CD-R/WI 2697)**

The system was validated for the **(b) (4)** study on 10/20/04. The "**(b) (4)**" **(b) (4)** indicates that "the PQR is the documented verification that the **(b) (4)** study data base meets business needs and functions as intended when used by properly trained system users." **(Exhibit #88, #89)**

No deficiencies were noted upon the review of validation test cases/records.

Each clinical investigator was provided with training and information prior to the initiation of the study at their respective sites. (See above question #2)

Protocol deviations and violations are recorded and tracked by the sponsor. These issues are followed-up with the clinical investigator and reported to the IRB and agency by letter. For example: a Protocol Deviation/Violations (PDV) report was completed for subject **(b) (6)** regarding the subject receiving a **(b) (4)** after the study surgery, which is a protocol violation. The PDV report indicates that the clinical site was notified by telephone and the corrective action consisted of retraining. An Adverse Event report was completed and the subject was withdrawn from the study. This issue also appears on the Protocol Non-Compliance Form (Table 23B) which was submitted to the agency. **(Exhibit #90)**

I verified the data entries against the CRF's for some of the following issues: Listing of Post Operative Site Specific Complications; Protocol Non-Compliance Violations; Intraoperative Exclusion Listing; and Reason for Failure at **(b) (4)** month Intervals etc. No discrepancies were noted.

In addition, I reviewed CRF's and Monitoring reports to assure that all protocol violations/deviations were being reported appropriately. No deviations were noted.

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Adverse events are reported in accordance with the firm's work instruction (WI-0433) See Exhibit #31 on CD)

The Study Manager is responsible for ensuring that all Clinical Investigators are aware of the requirements to report both anticipated and unanticipated adverse device effects.

The Clinical Investigator is required to report unanticipated adverse events within 10 working days to DePuy and IRB. (Exhibit #31)

Upon review of various unanticipated adverse device event report, I verified that these reports were submitted to the agency (via letter) within 10 working days upon notification; for example:

Site#	Adverse Event	Sponsor Notified	Reported to FDA
04	Femoral Neck Fracture	2/8/05	2/10/05
05	Femoral Neck Fracture	12/15/05	12/22/05

The protocol indicates that all adverse events, including the details of the nature, onset, duration and severity and relationship to the device should be recorded in the subject's CRF. Any severe adverse events or adverse device effects must be reported immediately by telephone or fax to DePuy.

I reviewed Monitoring visits and CRF's and noted that adverse events (AE's) were being documented and reported to the sponsor. Although the protocol does not required any times for reporting adverse events (not serious), I found that various AE's were being reported to the sponsor weeks and sometimes months after the events occurred. For example: an Adverse Event dated 7/20/05, involved mild to moderate swelling and pain in the left shin for subject (b) (6) however, the sponsor stamped the AE report as being received on 3/2/07.

Management indicated that in some cases the clinical sites were not always reporting adverse events since there were sometimes issues in ascertaining what is considered as an expected adverse event. However, during monitoring visits, these AE's were identified and reviewed with the site and subsequently submitted to the sponsor.

In addition, I noted that adverse event information is shared amongst each (b) (4) Study site.

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The firm submitted annual progress reports to the agency for the DePuy (b) (4) (b) (4) IDE Clinical Study on the following dates: 6/3/05; 5/19/06; and 8/2/07. (Exhibits #91-93, Exhibit #31 for procedure on CD-R WI- 0428)

The sponsor currently performs device accountability by way of work instruction WI-0437- Investigational Device Supply and Inventory Control. (Exhibit #31 on CD Revision B)

I was provided with a flow chart which shows the various steps for the shipment and return Investigational Devices. Upon manufacturing, the products are requested by the Study Manager for shipment to a particular investigational site. Since the request involves study products, the computer system assigns the request with a restricted code (type 7), and as a result, the device would only be shipped to the designated location (study site).

The study product is then shipped to a DePuy distribution office and subsequently delivered to the investigational study site by a DePuy Sales Representative. A re-order is requested in order to maintain the inventory at the clinical site.

Written procedures indicate that the "Administrative Assistant reviews orders at least (b) (4) and releases investigational devices to approved investigational sites." These releases are authorized by the Study Manager. Devices that are returned by the study site are maintained at the distributor's office and quarantined until they are returned to the warehouse. (Exhibit #94)

There were sometimes difficulties in tracking the disposition of study devices upon review shipping records. Even though the records indicate the dates the devices were shipped and returned, they do not readily reflect that transaction between the distribution site and finally the distribution site.

I was however able to track shipments more easily upon the review of a device accountability report which summarizes each shipment, order product, implant date and return date. I compared this list with the device accountability records for investigational sites #01 and #04; there were no discrepancies noted.

Since the study device components are individually available for commercial use, the final disposition of products involved the shipment to other locations for use.

Each shipment maintains an order number and lot number for the study devices, such as (b) (4) and (b) (4) (Exhibit #95) The study devices are assigned catalog numbers based on the Femoral and Acetabular implant sizes. For example the number associated with (b) (4) Femoral Implant size 32 is (b) (4) and (b) (4) Acetabular implant size 44 is (b) (4) (Exhibit #96)

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Each investigational site completes an Inventory Control Log which provides for the date of receipt, order number, lot number, the implant date, the reason for return, and date of return is recorded.

For example:

- Acetabular (50mm) device, catalog number (b) (4) order # (b) (4) lot (b) (4) was shipped from the sponsor on 10/20/04 per the Device Accountability Report. (Exhibit #95)
- The Inventory Control Log at the investigational site indicates that the device was received on 10/21/04. However, there are no individual or sub codes to identify the various devices with the same order number and lot numbers. However, one device was implanted on 7/14/05 and the three (3) remaining devices with the same information were returned to the sponsor on 2/28/06, due to the end of enrollment. The Device Accountability Report also indicates that various devices were returned on 2/28/06.
- Review of Investigational Device Inventory Control Audit Worksheets for each site did not show any discrepancies. (Exhibit #97)
- Upon review of the study device inventory control logs that were maintained at the site, I assured that there were no discrepancies in the accountability of devices. (Exhibit #98)

The investigational site also maintains a Device Implantation Record where the label from the actual product label is adhered to the records, so that the device can be linked directly to the patient.

Device accountability records are evaluated by the Study Monitor during routine visits and are reported in Monitoring Site Visit Reports. (See exhibit #49)

The firm is not currently involved in the humanitarian use of any devices.

According to Ms. Plouhar, the data for some subjects were not submitted to the agency due to the requirements involving the International protocol (b) (4), which allows subjects to participate in the study who meet certain criteria; such as, (b) (4) pre-operatively or post-operatively with in 2 years of the study. However this is an exclusion criterion for IDE (b) (4) therefore, information regarding subjects with these exclusionary identifiers were not submitted to the agency.

Ms. Plouhar provided me with the data and a written explanation regarding this issue. (Exhibit #99)

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OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

No FDA 483 Inspectional Observations List was issued.

REFUSALS

No refusals were encountered during the inspection.

GENERAL DISCUSSION WITH MANAGEMENT

At the close of the inspection, discussion was held with management regarding various issues; the following individuals were present during the discussion: Ms. Pamela Plouhar; Ms. Dee Furr; Ms. Vesna Zovkic; Ms. Keli Hankee; Ms. Kimberly Dwyer; Mr. James Sheets; and Ms. Laura J. Fazio.

- Whether the criteria used to terminate a Clinical Investigator site is adequate for sites that are repeatedly out of compliance and subsequently secured (for different situations). For example; even though compliance was secured after corrective actions were put into place at site# 01, on several occasions, there were new issues that arose during each monitoring visit. Based on the firms work instructions (SOPs), the site was not eligible for termination based on the criteria.
- Although there were work instructions (SOPs) for the general monitoring of clinical investigator sites, there was no specific monitoring plan for the (b) (4) study until approximately one year after the study was initiated.
- There were instances where anticipated/expected adverse events were reported weeks and sometimes months after the events occurred. The protocol does not require timeframes for the reporting of anticipated adverse events. However, discussion was held regarding the assurance that each CI site is appropriately identifying adverse events and whether any of the late ones could be deemed as serious (by the sponsor).
- There were sometimes difficulties in tracking the disposition of study devices after shipment upon review of the system records. Even though the system provides the dates shipped and returned, the devices are initially shipped to a distribution site which is subsequently provided to the clinical investigator by a DePuy representative; the records do not easily reflect this operation.

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ADDITIONAL INFORMATION

I ascertained that that site #01 used the (b) (4) study device off-label on non-study patients. According to Ms. Plouhar, DePuy was not aware that this CI was using the device off-label and discovered on 10/24/07. Correspondence from the investigational site shows in detail how this off-label usage was being performed by the staff:

“I contacted patients that are deemed by (b) (4) as candidates for (b) (4) and are scheduled for surgery. They are told that the (b) (4) device is non-FDA approved and that their surgery will be performed as an off-label usage outside of the IDE study. They are presented with the latest ICF (approved by the (b) (4) on 9/28/05) and are reminded that the ICF is for informational purposes only. They are advised to read the ICF as it outlines the procedures, benefits, risks and alternatives regarding the surgery, and these may apply to them regardless of their non-study status, because its is the same device. They are told that they do not need to complete/return the ICF; they only need to complete/return the Acknowledgment of Receipt of Research Subject Information and Consent Form (attached). They are reminded that, although they will not be part of the IDE study, we recommend regular x-ray and clinical follow-up (at the same time intervals) as we do to all total joint replacement patients. If they are unable to return to see (b) (4) for follow-up, we advise them to seek follow-up care with a local orthopedist of their choice.” (Exhibit #100)

According to Ms. Hankee, the acknowledgement of Receipt and Consent Form for this off-label usage was not prepared by DePuy. (Exhibit #100 page 5)

In addition, the protocol and labeling information indicates that the (b) (4) system device is for investigational use only. (Exhibit #5-7)

VOLUNTARY CORRECTIONS

At the close of the inspection, Ms. Plouhar showed me a draft of work instruction procedures which detailed the revised criteria for the termination clinical investigator sites that have various compliance issues.

EXHIBITS COLLECTED

1. DePuy Compliance-at-a-glance (47 pages)
2. DePuy Business Information and Organizational Chart (14 pages)
3. (b) (4) IDE Clinical Investigator Chart
4. (b) (4) Fact Sheet (42 Pages)

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5. Femoral Implant-Label Specifications (3 page)
6. MoM Standard Acetabular Cup-Label Specification
7. DePuy (b) (4) Head-Labeling (2 pages)
8. DHHS Memorandum re: (b) (4) 510k Pre-Market Notification dated (b) (4) (3 pages)
9. DePuy Clinical Research Employee Roles (3 pages)
10. Work Instruction WI 3832-Clinical Quality Assurance Audits of Clinical Investigator Sites (26 pages)
11. Consulting Agreement Letter dated 12/29/03 (b) (6) -11 pages
12. (b) (6) Curriculum Vitae (4 pages)
13. Clinical Consulting Agreement Letter dated 5/9/07 (b) (6) -2 pages
14. Consulting Agreement dated 2/16/04 (b) (6) -6 pages
15. Consulting Agreement (b) (4) (18 pages)
16. Consulting Agreement (b) (6) 14 pages
17. Research Agreement (b) (4) 9 pages
18. Consulting Agreement (b) (4) 5 pages
19. (b) (4) IDE Investigator Agreement IRB Approval Dates
20. Investigator and IRB List 2005-2 pages
21. Investigator and IRB List 2006-3 pages
22. Investigator and IRB List 2007-3 pages
23. Investigator and IRB List dated 12/17/07-2 pages
24. (b) (4) Certification of Approval (b) (6) dated 2/9/05-2 pages
25. (b) (4) Approval Letter dated 7/8/04-3 pages
26. (b) (4) Medical Affairs Approval Letter dated 10/5/04 (6 pages)
27. (b) (4) Approval Letter dated 5/13/04-2 pages
28. (b) (4) Approval Letter dated 12/16/04
29. E-mail re: (b) (6) withdrawal of site dated 4/21/05
30. Email re: withdrawal of (b) (4) site
31. DePuy Work Instructions on CD-R and corresponding Table of Contents (4 pages)
32. Monitoring Visits for (b) (4) (2 pages)
33. Pre-Investigational Visit Letter (b) (4) dated 7/6/04-2 pages
34. Pre-Investigational Visit Letter (b) (4) dated 1/31/05-3 pages
35. Pre-Investigational Visit Letter (b) (4) dated 9/30/04
36. Pre-Investigational Visit Letter (b) (4) dated 7/14/04-2 pages
37. Pre-Investigational Visit Letter dated 7/23/04
38. Pre-Investigational Visit Letter (b) (4) dated 8/12/04-2 pages
39. Pre-Investigational Visit Letter (b) (4) dated 7/26/04

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40. Monitor's Pre-Investigational Site Visit Report dated 5/21/04 (b) (4)-2 pages
41. Monitor's Pre-investigational Site Visit Report (b) (4) dated 10/6/04-2 pages
42. Monitor's Pre-investigational Site Visit Report (b) (4) dated 7/29/04-6 pages
43. Clinical Research Department Training Matrix (14 pages)
44. Work Instruction-Investigational Site Monitoring WI 0427 Rev. A dated 8/29/05-9 pages
45. Work Instruction-Site Visit Rev B dated 8/30/05-23 pages
46. Periodic Monitoring Site Visit Report (b) (4) dated 2/05 (5 pages)
47. Monitoring Site Visit Report (b) (4) dated 2/07 (7 pages)
48. Monitoring Site Visit Report (b) (4) dated 1/06 (6 pages)
49. Monitoring Site Visit Report (b) (4) dated 2/06-14 pages
50. Monitoring Site Visit Report (b) (4) dated 8/06-16 pages
51. Monitor's Pre-investigational Site Visit Report (b) (4) dated 7/04-6 pages
52. Periodic Monitoring Site Visit Report dated 3/10/05
53. Periodic Monitoring Site Visit Report dated 5/12,13/05-5 pages
54. Periodic Monitoring Site Visit Report dated 7/21,22/05-34 pages
55. Monitoring Site Visit Report dated 11/29/07-7 pages
56. Monitoring Plan IDE (b) (4) 3 pages
57. Subject Surgery Dates-5 pages
58. DePuy Memorandum dated 6/30/05-3 pages
59. Table 23A-Protocol Non-Compliance for various subjects
60. Table 23A-Protocol Non-Compliance-Deviations
61. Table 23A-Protocol Non-Compliance for various subjects
62. Table 23A-Protocol Non-Compliance for various subjects
63. Investigator Agreement-2 pages
64. Investigator Agreement-2 pages
65. Investigator Agreement-2 pages
66. (b) (4) IDE Meeting 9/22/03-6 pages
67. (b) (4) IDE Clinical Meeting Minutes 12/8/04-4 pages
68. DePuy (b) (4) System IDE Investigative Meeting 12/18/03-3 pages
69. Investigator Meeting dated 9/28/05-2 pages
70. Investigator Meeting dated 6/16/07-5 pages
71. Monitoring Site Visit Report dated 2/8,9/07
72. Monitoring Site Visit Report dated 10/16,17/06-6 pages
73. Monitoring Site Visit Report dated 5/29-31/07-6 pages
74. Table 23 A Protocol Non Compliance
75. Work Instruction WI-0363-7 pages

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76. Telephone Correspondence dated 6/29/06
77. DePuy Memorandum dated 6/8/05-2 pages
78. DePuy Memorandum dated 6/28/05-2 pages
79. (b) (4) Memorandum dated 6/9/05
80. Telephone Correspondence dated 1/28/05
81. Telephone Correspondence dated 4/2/05
82. Telephone Correspondence dated 4/28/05
83. Telephone Correspondence dated 5/5/05
84. DePuy e-mail dated 11/21/05
85. Telephone Correspondence dated 3/9/06
86. Data Issuance Form (DIF) dated 10/30/06
87. Work Instruction –Handling of Protocol Deviation & Violation (WI-2963)-8 pages
88. Computer Systems Validation (b) (4)
89. (b) (4) Clinical Study Database Performance Quality Report-4 pages
90. Protocol Deviation /Violations Form dated 10/1/07
91. Table 23B-Protocol Non-Compliance (0128)
92. Annual Progress Report Letter dated 6/3/05
93. Annual Progress Report Letter dated 5/19/06
94. Annual Progress Report Letter dated 8/2/07
95. Flowchart of Investigational Devices (shipment and return)
96. Femoral and Acetabular Implant catalog numbers
97. Investigational Device Inventory Control Audit Worksheet dated 7/29/04
98. Inventory Control Record dated 10/21/04
99. (b) (4) Report-10 pages
100. Email dated 1/29/08 re: off label usage of study device-5 pages

ATTACHMENTS

1. FDA 482-Notice of Inspection
2. CDRH Assignment

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ADDENDUM TO EIR

On 6/3/09, the ending date of the inspection was corrected in TURBO EIR in the header to show 2/11/08 instead of 1/28/08.



Myra K. Casey, Investigator