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December 21, 2016

Art Czabaniuk
District Director
Detroit District Office
U.S. Food and Drug Administration
300 River Place, Suite 5900
Detroit, Michigan 48207-4291

Subject: Response to FDA 483 Observations Issued to Zimmer Biomet, Warsaw North Campus, November 22, 2016

Dear Mr. Czabaniuk:

On November 22, 2016, U.S. Food and Drug Administration (FDA) Investigators Thomas Peter, Joseph Strelnik, and Suyang (Steve) Qin concluded an inspection of Zimmer Biomet, Inc. (FEI 1825034 – hereafter referred to as Zimmer Biomet) located in Warsaw, Indiana ("Warsaw North Campus" or "North Campus") and issued Inspectional Observations on the form FDA-483. Based on the extent of the FDA-483 observations, Zimmer Biomet requested and was granted an extension by FDA's Detroit District Office (DET-DO) to December 21, 2016, for the initial response. This written communication provides our initial response. A supplemental update will be provided to FDA on or before January 17, 2016, to share the outcome on four pending Health Hazard Evaluations (HHEs) as discussed in Section 3.2 below. We plan to submit our next full progress update to FDA on or before February 17, 2016.

1.0 Overview

We recognize and take seriously the significance of the observations in the FDA-483, are committed to taking all actions necessary to ensure that our systems are in compliance with FDA requirements, and are steadfast in our determination to ensure that our products are safe and effective. As is described in our attached detailed response, in addition to correcting the specific items listed in the FDA-483, we have taken and are continuing to take actions to address systemic issues. Significantly, we took immediate actions to address the quality culture at the site, (b) (4) , discussed in more detail in Section 2.2 below. Until the Zimmer Biomet merger on June 24, 2015, North Campus had been operating independently and with indications that its quality system was in substantial compliance. Once the merger was completed, the new Zimmer Biomet corporate management team conducted audits, learned of issues through the audits, and promptly initiated corrective actions. Improvements were well underway when FDA started the inspection and will continue with strong support, oversight and resources.

(b) (4)

(b) (4)

After the merger was closed, Zimmer Biomet Corporate directed corporate quality audits to be performed at the North Campus in the first half of 2016. These audits self-identified major compliance-related issues in areas such as design controls, sterile packaging, complaint handling, nonconforming material, and CAPAs. A remediation program with approved funding (b) (4) was established in July 2016 to address the systemic issues at the North Campus. This program self-identified CAPAs related to 7 of the 483 observations and 6 of the discussion points prior to the start of the inspection. At the start of the FDA inspection, the remediation program was in the initial phase of execution. Remediation efforts were accelerated as additional issues were identified by FDA during the inspection. Rather than wait for the issuance of the FDA-483 to plan and take action, we immediately took steps to correct and improve various aspects of the North Campus quality management system. Immediate containment and investigation actions to date included the initiation of (b) product holds,(b) health hazard safety evaluations, and (b interim control documents. (b) (4) . After the FDA inspection concluded, the North Campus remediation efforts were greatly expanded and will be covered under a master CAPA program called (b) (4) , discussed in Section 4.0 below.

2.0 Zimmer Biomet Corporate Oversight

2.1 Corporate Audits

Since the merger, the Zimmer Biomet Corporate Audit function has completed (b) audits at legacy Zimmer sites, (b) audits at legacy Biomet sites, and (network process audits, for a total of (b Corporate audits (July 2015-December 2016). All Zimmer Biomet production sites have been audited (b) (4) . The table below lists the Corporate Audits focused on the North Campus.

Post-acquisition Corporate Audits of Warsaw North in the First Half of 2016
Corporate Complaints Process Audit: Completed by the Corporate Audit Team and the audit report was issued on March 31, 2016. The audit focused on the Warsaw North complaint handling process and identified 6 major and 2 minor observations which were addressed as part of the post market surveillance remediation program CAPAs.
Corporate Design Controls Audit: (b) (4) audit report was issued on April 13, 2016. This audit was requested to evaluate the applicability of the lessons learned from the Zimmer Warsaw West Campus design control 483 observations. The audit identified 4 critical and 15 major observations which resulted in the establishment of the design controls remediation program CAPAs.
Corporate General QMS Audit: Completed by the Corporate Audit Team which (b) (4) (b) (4) The report was issued on June 7, 2016 and identified 15 major and 5 minor observations which were addressed using the CAPA system.

(b) (4) , an action item was created to perform a network-wide Corporate Audit of all Zimmer Biomet sites with end of line

operations (cleaning, sterile packaging, and sterilization) in order to assess the issues identified by the FDA inspection of the North Campus. A detailed audit protocol will be created to ensure consistency of the audit across all the sites and include an on-site audit of the completed audit report (b) (4) . (b) (4) .

2.2 Management Changes

The following management changes have been implemented by Zimmer Biomet to address Quality Management System performance issues noted at the Warsaw North Campus, along with underlying quality culture issues now recognized.

Management Position	Summary of Change
Senior Vice President of Global Operations and Logistics Team	(b) (4) . Adrian Furey, a legacy Zimmer leader, was named the interim leader.
Vice President of Quality Assurance responsible for the Warsaw Sites	(b) (4) . Christopher Slimak was named as the new leader for the Warsaw sites.
Quality Assurance Director responsible for the North Campus	(b) (4) . Jeff Gensler was named as the new leader for the North Campus.
Compliance Director responsible for the Biomet Network	(b) (4) . This role now resides in the Zimmer Biomet Corporate organization and Holly Seppanen is now the responsible Compliance Director.
Quality Assurance Director responsible for the Warsaw Post Market Surveillance (PMS) and Complaint Handling Group	(b) (4) Barbara Ruf was named as the new leader for the Warsaw PMS Group.

2.3 Resource Commitment

a. Remediation funding for the North Campus in excess of (b) (4) was approved in (b) (4) by the CEO. After the FDA inspection, the total remediation budget estimate increased by (b) (4) . The business plan for 2017 has (b) (4) committed of the total (b) (4) estimated budget for (b) (4) through 2018.

b. Post Market Surveillance remediation program resources were approved in May 2016, which added (b) (4) resources in 2016 with an additional commitment of (b) (4) resources in 2017 to support (b) (4) . The resource approvals included new (b) (4) positions in support of the complaint handling process.

c. (b) (4) Quality Assurance (b) (4) resource additions (b) (4) (b) (4)) were approved for the base business in July 2016. (b) (4)

(b) (4)

d. The Warsaw Operations Group was restructured in December 2016 to (b) (4) . (b) (4) . Previously, manufacturing engineering and production line supervision resided under one Vice President leader.

3.0 Corrective actions

3.1 Immediate Actions taken during the Inspection to address FDA Observations

a. Below are the summary key actions taken during the inspection, demonstrating that Zimmer Biomet is fully committed to addressing the additional issues identified by FDA.

i. Product ship hold (16-064) was issued on September 29, 2016 to stop shipments of all final product cleaned, sterile packed, and sterilized at the Warsaw North Campus. After investigations were completed and documented justifications were prepared and approved, initial product ship hold releases under interim controls first began on October 21, 2016. Product holds were released only after detailed justifications were documented to address product safety and effectiveness using the enhanced hold process implemented during the inspection.

ii. (b) (4) interim control documents were implemented during the FDA inspection to address process control issues raised by FDA. The interim controls were established to support continuing manufacturing while the extensive corrective actions are underway. Copies of the (b) interim controls were provided to and reviewed by the FDA inspection team at the end of the inspection.

iii. (b) (4) final cleaning for metal products was stopped ((b) (4) . The final cleaning for metal products was modified (b) (4) .

iv. The main cleanrooms for (b) (4) were requalified and process monitoring was enhanced to align with the (b) (4) standards.

v. Sterile product cleaning and packaging process monitoring was enhanced to align with the testing standards required on the (b) (4) .

vi. (b) (4)

3.2 Product Safety (HHEs)

As of December 20, 2016, a total of (b) Health Hazard Evaluation Determination (HHED) forms were initiated to address FDA observations and discussion points raised during the inspection. Of these (b) were elevated to full Health Hazard Evaluation (HHE) which includes (b) (4) (b) (4) . HHEs have been completed for (b) (4) issues under evaluation. HHE reviews completed to date by the Global Recall Committee have not resulted in any field actions. The pending (b) HHEs listed below (b) (4) (b) will be provided to FDA (b) (4) .

483 Obs	Pending HHE Details	Product Hold
(		
b		
)		

In addition, there were (b) HHEDs initiated from CA-02719 that was opened prior to the FDA inspection. This CAPA is part of the Observation 4 response on design controls.

3.3 Interim Controls and Product Holds

3.3.1 Interim Controls

Interim controls have been established as an immediate action to contain issues and to support continuing manufacturing while extensive corrective actions are underway. These interim controls were deployed as part of the CAPA investigations and were a key element of Zimmer Biomet's decision to release certain product holds after the (b) (4) (b) product shipment hold period (b) (4) . The following key process controls were implemented as part of the deployed interim controls.

- Cleaning process enhancements implemented to ensure that product released satisfies the cleaning standard utilized (b) (4) (i.e., the ZES 4N-02 (b) (4)
- Sterile product (b) (4) was eliminated as an acceptable final clean process, replaced by (b) (4) cleaning systems with enhanced process monitoring
- Cleanroom controls and routine environmental monitoring were enhanced to align with (b) (4) Standards
- Sterile packaging process data recording and process monitoring were enhanced to align (b) (4) Standards

Subsystems Impacted by Interim Control	Quantity of Interim Controls Deployed
Cleaning Process	(b
Cleanroom Environmental Controls	(
Sterile Packaging	(
Complaint Handling	(
Nonconforming Material	(
Gage Controls	(
Production/Process Controls	(
QMS Miscellaneous	(
Total Deployed	(b

3.3.2 Product Holds

Product holds have been issued to support containment of product as part of the CAPA investigation into the quality observations identified. The quality hold process was updated to align with the (b) (4) procedure to require documented information when placing and releasing holds. Product hold releases require evaluation and disposition using the nonconforming material process requirements. Since the start of the inspection, (b) quality holds have been deployed (b) (4)) as part of investigations related to the FDA inspection. Each 483 observation response provides details on any associated product hold(s) initiated as part of the corrective action. Major product holds issued during the inspection as part of the quality investigation phase were related to the following processes: (b) (4)

4.0 (b) (4) Remediation Program for the North Campus

Zimmer Biomet initiated (b) (4) , (b) (4) (b) (4) .

a. The (b) (4) remediation framework includes (b) focused work-streams as listed in the table below. Each work-stream will have a detailed project charter (b) (4) .

(b) (4)	Remediation Work-streams		
			(b) (4)

i. Target completion date for the (b) (4) Program is (b) (4) . The design remediation scope will likely extend into the second half of 2018 based on the Project Trident design history file (DHF) remediation experience. (b) (4) will be utilized (b) (4) to complete the project (b) (4) .

ii. (b) (4) . (b) (4) .

iii. All processes at the North Campus will be brought up to current process validation standards (b) (4) .

1) All processes requiring action will be revalidated to current process validation standards at the site, revalidated as part of a product transfer, or the associated devices will be obsoleted. (b) (4)

2) End of line operations (b) (4)) will be moved (b) (4)

3) (b) (4)

iv. All design history files (DHFs) will be evaluated and remediated to current design control standards or obsoleted (b) (4) . Any DHFs pending remediation (b) (4) .

v. The following Quality Management System (QMS) audits and independent reviews will be completed as part of (b) (4) :

1) Additional baseline QMS audits at the North Campus will be performed (b) (4) to review subsystems not covered by the Corporate Audits performed in the first half of 2016. These audits will be completed by Corporate Audit (b) (4) .

2) QMS subsystem audits will be completed (b) (4) These audits will be completed by Corporate Audit (b) (4) .

3) A full QMS audit will be performed at the completion of (b) (4) ((b) (b) (4)

4) Independent reviews of completed remediation work will be completed by QMS auditors and reports will be issued. Independent reviews will be performed each quarter and the results will be reported to the project steering committee.

5.0 Zimmer Biomet Corporate Commitment to Quality Excellence

After the Zimmer Biomet merger closed in June 2015, actions were initiated to establish the Zimmer Biomet quality standards for the network as part of the Quality Excellence Plan. The Quality Excellence Plan is a multi-year plan to incorporate recognized industry best practices (e.g., Case for Quality initiatives) (b) (4) . (b) (4) .

Zimmer Biomet Executive Management reviewed the multi-year Quality Excellence plan in

December 2015 to confirm commitment and funding for the 2016 installment. (b) (4) A summary of the Quality Excellence Plan was provided to FDA DET-DO on February 10, 2016 (b) .

At the time of the Warsaw North Campus FDA inspection, Zimmer Biomet was into year one of the network Quality Excellence enhancements. During the FDA inspection, some elements of the Quality Excellence plan already deployed at the Warsaw North Campus (e.g., standardized HHE process, Global recall procedure, Corporate Quality Management Reviews, and the network monthly global quality report) were reviewed with no FDA observations. Other observations by FDA were related to elements that are still pending deployment as part of the multi-year plan (b) (4) and will be accelerated as part of the 483 response corrective actions and (b) (4) . An update on the year-one network Quality Excellence deployments is included in the tables below along with the 2017 plans.

2016 Network Quality Excellence Program Accomplishments	2017 Network Quality Excellence Program Planned Actions
Global QMS System Harmonization	
• For 2016, a top level Corporate quality goal was to complete (b) (4) across the network. The 2016 goal was achieved with over (b) network implementation actions completed. • Year one of the Global QMS system deployment addressed global alignment on key procedures including Complaints, CAPA, SCARs, HHE, Global Recall Process, (b) (4) Global Quality KPI reporting, and Management Review. • For CAPA, SCARs, and complaints, the Zimmer Biomet network is now harmonized with the corporate procedures and using the standardized (b) (4) software modules to manage the records.	• Complete at least (b) QMS harmonization elements across the network in 2017 as part of Quality Indicator (b) improvement • Deploy at least (b) new (b) software applications: ((b) (4)) • Deploy standardized network electronic documentation system for document control at pilot sites
Design Excellence	
• Global design control procedures have been drafted and are in the final peer review process. (b) (4) • Capital funding has been approved (b) (4) to implement an industry established DHF and design control requirements management software (b) (4) As part of the Warsaw Biomet DHF remediation (CAPA CA-02719), the DHF files will be remediated (b) (4) (b) (4)	• Deploy standardized design control and risk management documents across the network • Deploy the (b) (4) software to support (b) (4) remediation • Deploy the (b) (4) software to pilot with Zimmer Warsaw West design controls
Regulatory Compliance Excellence	
• Released a new CAPA procedure for the network to support CAPA processing in the CAPA software tool (b) (4) • Drafted CAPA Academy training material to support standardized network CAPA essential training. The CAPA Academy training material deployment will start (b) (4) . • Progressed Zimmer product shipping controls to align with Biomet licensing confirmation process (b) (4)	• Deploy CAPA Academy training material to support standardized network CAPA essential training • Deploy initial phases of standardized (b) (4) software to automate confirmation of product shipments with regulatory clearances/registrations
2016 Network Quality Excellence Program Accomplishments	**2017 Network Quality Excellence Program Planned Actions**

Supply Chain Excellence	
• The following plant network optimization changes have been announced as part of Quality Excellence: ○ (b) (4) • Global Supplier Conference was held in April 2016 with attendance by over (b) network suppliers to review Zimmer Biomet supplier controls and associated quality standards.	• Complete product network optimization product transfers to align with centers of excellence plan • (b) (4) • Deploy (b) (4) e at (additional network sites • Progress on Class A certification efforts in the network with at least (sites earning Class A certification. Class A is part of the (b) (4) checklist for business excellence.
Quality Culture	
• A new top level quality indicator metric for quality excellence was created for 2016 with (b) improvement targets for QMS harmonization, External Audits, Recalls, and product in-process NCR rates. This metric was reported (b) (4) in the global quality report and reviewed (b) (4) Executed a comprehensive communication program through routine management reviews, town halls, leadership forums, Zimmer Biomet news updates, postings, electronic displays, and network e-mails to support Team Member awareness and engagement with Quality Excellence. • Completed a global company survey that included (b) questions specifically related to quality. This feedback was used to address actions with our (b) (4) (b) (4) Team Members provided survey feedback which was an (b) participation rate.	• Continue top level quality indicator metric for quality excellence with (b) improvement targets for QMS harmonization, external audits, recalls, and product in-process NCR rates (at least (b) improvement targets) • Deploy a new network learning management system (b) (4) software system to create a single (b) software system for Zimmer Biomet • Establish a network CAPA award/recognition program • Continue comprehensive quality culture awareness communications plan

6.0 Final Discussions

In addition to the observations on the FDA-483, during discussions with Warsaw North Management at the inspection closeout meeting, FDA investigators made recommendations and identified opportunities for improvement. Zimmer Biomet takes these recommendations and opportunities for improvement seriously. In the attachments, please find our responses to the 483 observations, followed by our responses to the management discussion points.

(b) (4)

We would like the opportunity to meet with FDA to discuss our progress made to date and the planned actions outlined in the attached response. We will contact you in early January to find a mutually convenient time to meet.

If you have any questions or need any clarification, please do not hesitate to contact me at david.kunz@zimmerbiomet.com or 952-378-7718.

Respectfully,

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Zimmer Biomet

Cc:

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FDA Observation 1

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FDA Observation #1

A process whose results cannot be fully verified by subsequent inspection and test has not been
adequately validated according to established procedures.

Specifically,

***Note 1:** This is a repeat observation from the FDA inspection dated 6/16/2014 to 6/30/2014.*

***Note 2:** This process validation observation comprises the following 9 parts:*

- ***A.*** (b) (4) ***sterilization validation***
- ***B.*** (b) (4) ***sterilization validation***
- ***C. Sterile packaging process validations***
- ***D.*** (b) (4) ***water system validation***
- ***E. Validation of*** (b) (4) ***cleaning process governed by WIG0035 (Rev. 4, effective 9/19/2011) for knee femoral implants***
- ***F. Validation of*** (b) (4) ***cleaning process governed by work instruction WIG0151 (Rev. 1, effective 4/21/2015) for metal hip, extremities, knee, trauma, microfixation, and sports medicine devices***
- ***G. Validation of*** (b) (4) ***cleaning process governed by work instruction WIG0150 (Rev. 3, effective 5/5/2016) for devices made of ultra-high-molecular-weight polyethylene (UHMWPE)***
- ***H. Validation of*** (b) (4) ***cleaning process governed by work instruction WJS0086 (Rev. 3, effective 10/13/2015) for sports medicine and microfixation devices manufactured out of Lactosorb® and PEEK materials***
- ***I. Ultra-high-molecular-weight polyethylene (UHMWPE)*** (b) (4) (b) (4) ***molding process validation***

Observation 1 Investigation and Response:

On December 15, 2016, Zimmer Biomet initiated CAPA CA-03121 (*Systemic Improvements to Process Validation Systems*) to address system-wide issues concerning process validation (see attachment 1-A, *CAPA CA-03121 CAPA Summary*). CA-03121 is currently in the Investigation (Root Cause/Action Plan) Phase.

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Per CAPA CA-03121, Zimmer Biomet will evaluate all procedures, forms, and work instructions associated with the process validation system at the Warsaw North Campus to ensure that the quality system is compliant with the requirements of 21 C.F.R. § 820.75. Specifically, Zimmer Biomet will ensure that procedures, forms, and work instructions address:

1. (b) (4)

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11. (b) (4)

Zimmer Biomet will revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of each of the foregoing quality system requirements. In addition, Zimmer Biomet will ensure that the entire process validation system conforms to the requirements of 21 C.F.R. § 820.75. Zimmer Biomet will leverage the newly revised process validation procedures, forms, and work instructions recently and successfully implemented at the (b) (4) (b) (4) (b) (4), as appropriate for the process at the Warsaw North Campus (see attachment 1-B, IC014, Process Validation Interim Control). Zimmer Biomet will address all deficiencies identified throughout Observation 1 and any other gaps identified by Zimmer Biomet during the investigation of CAPA CA-03121.

(b) (4)

(b) (4)

(b) (4)

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Completed Actions:

No.	Action	Completion Date
1-1	IC 014, Process Validation Interim Control (see attachment 1-B)	December 8, 2016
1-2	Initiated CAPA CA-03121 to address the system-wide issues concerning process validation identified in Observation 1 (see attachment 1-A).	December 15, 2016

Planned Actions:

No.	Action	Completion Date
1-3	Evaluate all procedures, forms, and work instructions associated with the process validation quality system at Warsaw North Campus to identify any additional gaps in quality system to the requirements of 21 C.F.R. § 820.75, in addition to the deficiencies identified in Observations 1(A) through 1(I).	(b) (4)
1-4	Complete CA-03121 Root Cause/Action Plan Phase	(b) (4)
1-5	Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of quality system requirements.	Target completion date to be reported in a future update
1-6	Complete CAPA CA-03121 Implementation Phase.	Target completion date to be reported in a future update
1-7	Verify effectiveness of CAPA CA-03121 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #1(A)

A. The "metals" family sterilized by (b) (4) has not been adequately validated to provide objective evidence that sterilized devices meet a SAL of (b) (4) as purported by the validation and revalidation reports. All revisions of *SOP 9.4.2:* (b) (4) *Sterilization Validation Method* effective since at least 12/7/1999 require validations to comply with the ISO 11137 standard.

Preventive action #PA-00538 was initiated on 1/7/2016. As of 9/14/2016, the problem statement read: "The scope of the PA is to capture the development of multiple (b) (4) sterilization product families and the supporting activities." The preventive action was in-progress at the time of this inspection to re-define existing (b) (4) families such as the "metals" family using the principles of ISO 11137. As of 10/25/2016, the "metals" family comprised approximately (b) (4) unique item numbers that were distributed between 7/1/2014 and 10/13/2016. These (b) (4) item numbers include devices such as Taperloc porous femoral hip implants *(e.g.,* item number 103205) and Biomet porous tibial tray implants *(e.g.,* item number 141213).

i. The criteria that clearly define the metals family have not been adequately documented as required by ISO 11137. The initial validation, revalidation, and subsequent assessments for adopting devices into the metals family do not substantiate the product scope of approximately (b) (4) item numbers comprising the family as of 10/25/2016 that have been distributed between 7/1/2014 and 10/13/2016. Specifically:

a. The initial validation of the metals family by the (b) (4) method (Validation #126) and revalidation (Validation #282) were approved on 5/27/2004 and 1/5/2009, respectively. Neither validation defines a product scope. In each case, simulated product (sample CP550157) was tested.

b. The product scope represented by the simulated product had not been defined at the time of the validations. During the "Equivalency Justification of Simulated Product for Use in Sterility Validation" for CP550157 (approved 3/17/2003), the scope was (b) (4)

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(b) (4) ." During the study, your firm chose five different devices (item numbers) for comparison against the simulated product. However, a comprehensive product scope intended to be represented by the simulant was not documented.

c. Assessments for adopting devices into the metals family have routinely not been documented. Approximately (b) (4) unique item numbers belonging to the metals family (b) (4)) have no documented assessment of whether they introduce a greater sterilization challenge than the simulant. Approximately (b) (4) devices with these (b) (4) item numbers were distributed by your firm between 7/1/2014 and 10/13/2016.

It is unknown how many devices comprised the metals family at the time the simulant was approved on 3/17/2003; however, your firm did not begin manufacturing approximately 1,466 of the 4,156 unique item numbers until after that date. (b) (4) item numbers (b) (4) have no documented assessment associated with them. Approximately (b) (4) devices with these (b) (4) item numbers were distributed by your firm between 7/1/2014 and 10/13/2016.

ii. Your firm's bioburden monitoring and dose audit program for the metals family is inadequate because it utilizes simulated product that does not represent approximately (b) (4) item numbers ((b) (4) comprising the family. Consequently, the continued effectiveness of the (b) (4) sterilization dose has not been adequately demonstrated as required by ISO 11137.

Your firm's Associate Director of Sterilization Technology explained that (b) (4) for metal devices prior to packaging and sterilization. At the time the simulated product was approved on 3/17/2003, the only passivation lines commissioned in Building A were located (b) (4)). As of 9/12/2016, the simulated product (CP550157) continues to be (b) (4) (b) (4) before being inspected in (b) (4) and packaged in (b) (4) .

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From the time the simulated product was approved on 3/17/2003 to 10/25/2016, the metals family has evolved into approximately (b) (4) unique item numbers that are (b) (4) in at least (b) (4) work centers throughout (b) (4) From there, the devices follow different process flows prior to packaging in a cleanroom environment that may affect product bioburden levels. For example:

Device	(b) (4) (b) (4) (b) (4)	Subsequent Steps
Vanguard CR Knee porous femoral components (e.g., item number 183056)	(b) (4)	• Inspection ((b) (4)) • Assembly ((b) (4) • Inspection ((b) (4)) • Packaging ((b) (4))
Vanguard XP CR tibial trays (e.g., item number 195273)	(b) (4)	• Inspection (b) (4)) • Packaging (b) (4))
Freedom Hip System constrained modular head component (e.g., item number 110025131)	(b) (4)	• Inspection (b) (4) • Packaging (b) (4)
Regenerex acetabular shell (e.g., item number PT-126272)	(b) (4)	• Rinsing (b) (4)) • Inspection (b) (4)) • Packaging ((b) (4))

As stated previously, the simulated product does not adequately represent approximately (b) (4) item numbers comprising the family. Approximately (b) (4) devices with these (b) (4) item numbers were distributed by your firm between 7/1/2014 and 10/13/2016.

iii. A review of the metals family and the simulated product that represents the family has not been adequately documented at least annually as required by ISO 11137. Approximately (b) (4) devices having the (b) (4) item numbers comprising the family were distributed by your firm between 7/1/2014 and 10/13/2016.

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a. Your firm could not provide evidence that reviews were held prior to 2014.

b. During the annual reviews held in 2014 and 2015, your firm determined that "the product family and the product to represent that family in dose audit testing remain valid." The rationale provided in the reports is not adequate. Specifically:

1. **The reports included trend analysis of simulated product bioburden, which determined "a stable trend over the life of the product family." As discussed in Part B(ii) of this observation, approximately (b) (4) of the devices belonging to the metals family are not adequately represented by the simulated product.**

2. **The reports also included trend analyses of (b) (4) product bioburden testing performed according to *QP0020: Routine Bioburden Sampling—Finished Devices* (Revs. 13 and 14, effective 5/11/2011 and current as of 11/17/2016). The trend analysis within each report determined that "the (b) (4) averages for this family have demonstrated control over time." Per *QP0020,* your firm tests (b) (4) devices for bioburden (b) (4) , of which five or six come from the metals family. The practice of randomly sampling five or six disparate products per (b) (4) and averaging their bioburden results is statistically invalid and does not comply with ISO 11137 requirements for bioburden monitoring. Notably, there have been two instances since 2014 in which "porous hip" devices from the metals family failed to meet (b) (4) bioburden acceptance criteria.**

3. **The reports claim that "Since the establishment of the product family, there has been no significant change to the manufacturing processes that may contribute to higher bioburden levels. The processes, equipment, environments, and operator involvement have remained fundamentally the same." Part B(ii) of this observation describes how the**

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environments to which devices are exposed after (b) (4) have changed over time.

Observation 1(A) Investigation and Response:

On October 20, 2016, Zimmer Biomet initiated CAPA CA-02978 to investigate and address observations articulated during the inspection and later detailed in Observation 1(A) regarding deficiencies surrounding the availability of objective evidence supporting validation of the sterilization process to ensure a Sterility Assurance Level ("SAL") of (b) (4) sterilized products (see attachment 1A-A, *CAPA CA-02978 Summary)*. While the observation specifically cited the "Metals" sterile product family, (b) (4) (b) (4)

(b) (4)

Zimmer Biomet determined (b) (4) that sterile product families, and (b) (4) (b) (4) Since this Preventive Action was not completed prior to the FDA inspection, and Zimmer Biomet now acknowledges that it should have been documented as a corrective action (see Observation 5(B) regarding the use of Preventive versus Corrective Actions), PA-00538 has been voided and replaced by CAPA CA-02978. In addition to addressing the deficiencies articulated in Observation 1(A) for the "Metals" sterile product family, this CAPA will address the following identified issues for all (b) (4) sterilized product:

- The criteria for defining sterile product families have not been adequately documented (identified in Observation 1(A)(i)).
- The scope of products covered by existing validations/sterile product families has not been documented (identified in Observation 1(A)(i)(a)).
- A simulated product was used to represent some of the sterile product families (including "Metals") without assessing whether the products included in the family

represented a greater sterilization challenge than the simulant (identified in Observation 1(A)(i)(b)).

- (b) (4) . Observation 1(A)(i)(c) notes that (b) (4) % of the "Metals" sterile product family does not have documented assessments for inclusion in the family. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)
- (b) (4) , (b) (4) Consequently, the continued effectiveness of the (b) (4) sterilization dose has not been adequately demonstrated as required by ISO 11137 (identified in Observation 1(A)(ii)).
- Periodic reviews, performed at least (b) (4) , to ensure that product families and product/simulant used to represent each product family remain valid have not been adequately documented prior to 2014 (identified in Observation 1(A)(iii)(a)). Furthermore, the reviews conducted in 2014 and 2015 drew conclusions from bioburden data that was not representative of the process and failed to acknowledge the potential impact of changes in the manufacturing processes since inception of the sterile product families (identified in Observation 1(A)(iii)(b)).
- The practice of randomly sampling five or six disparate products per (b) (4) and averaging their bioburden results for trend analysis is statistically invalid and does not comply with ISO 11137 requirements for bioburden monitoring (identified in Observation 1(A)(iii)(b)(2)).

CA-02978 currently is in the Investigation (Root Cause/Action Plan) phase.

Zimmer Biomet has taken several actions to address the impact of the findings in Observation 1(A) while long-term corrective actions are developed and implemented. First, as explained in the cover letter to this response, during the inspection Zimmer Biomet implemented (b) (4) , to (b) (4) (b) (4) .

(b) (4) , Zimmer Biomet initiated a Health Hazard Evaluation-Determination ("HHED") to assess the potential product safety impact of the gaps in (b) (4) sterilization validations noted in Observation 1(A) (see attachment 1A-C, *HHED #10-2016-036*). HHED #10-2016-036 was approved (b) (4) . (b) (4)

(b) (4) HHE #2016-0296 was reviewed (b) (4) (b) (4) .

(b) (4)

The correction of the deficiencies identified in Observation 1(A) will continue, and carry to completion, the same approach developed for the original preventative action (PA-00358) for all (b) (4) sterilized product families (b) (4) (b) (4) Under the original PA (PA-00358), the (b) (4) approach to creating (b) (4) sterile product families was established and led to the creation of (b) (4) separate sterile product families compared with the original (b) (4) established (b) (4) sterile product families (see attachment 1A-E, *SOP 9.4.2* (b) (4) At the time of the inspection (b) (4) of these validations were complete and another (b) (4) were in various stages of execution. This approach is based on the requirements established in ISO 11137-2 and includes the following key features:

- Criteria for defining sterile product families will comply with the requirements of ISO 11137-2 and will consider product-related variables that affect bioburden (b) (4) In establishing sterile product families on the Warsaw North Campus, a (b) (4) approach will be utilized. (b) (4) , for the list of defined work centers and scope list of products). A specification for each product family will be documented and (b) (4) .
- All sterile product families will include a defined scope (b) (4) . This will ensure that the finding in Observation 1(A)(i)(a) is addressed.
- Most of the sterilization validations will utilize a (b) (4) as defined in ISO 11137-2, to represent the sterile product family for bioburden monitoring and dose

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auditing. (b) (4) This will ensure that the finding in Observations 1(A)(i)(b) and 1(A)(ii) are addressed.

- As required in ISO 11137-2, and further defined in , a documented review of all sterile product families will be completed (b) (4) to ensure that the product used to represent the family remains valid. (b) (4) . The requirements for the (b) (4) review will be formalized in the appropriate standard operating procedure. This will ensure that the findings in all subparts of Observation 1(A)(iii) are addressed.
- (b) (4) . Routine bioburden testing will be performed (b) (4) on the (b) (4) will be performed in conjunction with the sterilization dose audit as required in ISO 11137-2. This will ensure that the finding in Observation 1(A)(iii)(b)(2) is addressed.
- Product adoptions will be performed (b) (4) . A standard operating procedure will be documented to reflect the product adoption requirements. This will ensure that the finding in Observation 1(A)(i)(c) is addressed.
- (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

In future updates to this response, Zimmer Biomet will provide details of, and timelines for, the corrections and corrective actions that are identified during the Investigation (Root Cause/Action Plan) phase of CA-02978.

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Completed Actions:

No.	Action	Completion Date
1A-1	(b) (4)	September 29, 2016
1A-2	Opened CAPA CA-02978 (see attachment 1A-A).	October 20, 2016
1A-3	Initiated Health Hazard Evaluation ("HHE") to assess the potential product safety impact of the gaps in (b) (4) sterilization validations (see attachment 1A-C).	October 25, 2016
1A-4	Identified product scope covered by the previous preventative action (PA-00358) and now covered by CAPA CA-02978 (see attachment 1A-F).	November 11, 2016
1A-5	Completed Health Hazard Evaluation ("HHE") to assess the potential product safety impact of the gaps in (b) (4) sterilization validations (see attachment 1A-D).	December 16, 2016
1A-6	(b) (4)	December 20, 2016

Planned Actions:

No.	Action	Completion Date
1A-7	Complete CAPA CA-02978 Investigation (Root Cause/Action Plan) phase	(b) (4)
1A-8	Complete correction activities so all (b) (4) sterilized products are part of a validated sterile product family that complies with the requirements in ISO 11137-2.	B.Target completion date to be reported in a future update
1A-9	Complete CA-02978 Implementation Phase.	C.Target completion date to be reported in a future update
1A-10	Verify effectiveness of CA-02978 and close CAPA.	D. Target completion date to be reported in a future update

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FDA Observation #1(B)

A. The validation of (b) (4) sterilization (b) (4) (Validation #79, approved 3/14/2003) fails to provide objective evidence that devices are sterilized with an SAL of (b) (4) as purported by the validation report, which claims conformance with ISO 11135. (b) (4) is used to sterilize sports medicine, trauma, and microfixation devices manufactured from (b) (4) resorbable material, (b) (4) and other materials. Specifically:

a. The (b) (4) cycle run during the validation (Load #01283-C) failed to conclusively demonstrate that the IPCDs and EPCDs present a greater sterilization challenge than the natural product bioburden at all locations throughout the sterilization load. One of the 30 product samples tested positive for microbial growth without further investigation.

b. Justification that the simulated product used during the validation (lot number M770070, item number undefined) presents an equal or greater sterilization challenge than the most difficult to sterilize product was not documented. The initial validation did not did not provide a product scope, but your firm estimated that approximately 211 unique item numbers were part of the sterilization family at that time.

c. The validation does not provide evidence that product sterility samples and IPCDs were placed in the most difficult-to-sterilize locations in the load during the (b) (4) cycle and (b) (4) cycles. Products sterilized by (b) (4) are packed into (b) (4) totes (b) (4) During the (b) (4) cycle and (b) (4) cycles, your firm placed (b) (4) product samples and (b) (4) IPCDs within (b) (4) totes throughout the sterilization load. However, the location within each tote was not defined.

d. All (b) (4) requalifications conducted between 2004 and 2015 lack objective evidence that a product SAL of (b) (was achieved. Specifically:

i. During requalifications in 2004 and 2005, your firm tested product samples in addition to IPCDs and EPCDs for sterility. In each year, one of the product samples tested positive whereas all IPCDs and EPCDs tested negative. The documented rationale within each investigation (dated 12/29/2004 and 5/24/2005) to "invalidate" the sterility

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failures is not adequate because the location of the product sterility samples and IPCDs within each tote were again not defined. The requalification results in 2004 and 2005 indicate that the natural product bioburden may present a greater sterilization challenge than the IPCDs and EPCDs used at that time.

ii. **During requalifications since at least 2008, your firm has assembled IPCDs in a manner that apparently renders the (b) (4) than in earlier requalifications and the initial validation. Products sterilized by (b) (4) are packaged in configurations such as a (b) (4) , which in turn is packaged in a (b) (4) . During the initial validation and requalifications in 2004, 2005, 2006, and possibly 2007, IPCDs were assembled by placing (b) (4) (b) (4) with the product. Beginning in 2008, IPCDs were assembled by (b) (4) A comparative resistance study has not been performed to demonstrate that the current-day IPCD presents an equal or greater sterilization challenge than the most difficult to sterilize product.**

e. **The initial validation utilized a (b) (4) load whereas the 2004 requalification utilized a (b) (4) load without documented justification. All revisions of *SOP 9.4.4* effective since 12/7/1999 require (b) (4) sterilization cycles to be requalified on an (b) (4) basis.**

Between 7/1/2014 and 10/13/2016, your firm distributed at least (b) (4) devices that were sterilized by (b) (4)

Observation 1(B) Investigation and Response:

(b) (4)

(b) (4)

(b) (4)

(b) (4)). (b) (4)

Zimmer Biomet now acknowledges that nonconformances to (b) (4) (b) (4) should have been documented and addressed as a Corrective Action instead of as a Preventive Action. Improper creation of a Preventive Action instead of a Corrective Action is addressed in Zimmer Biomet's response to FDA Observation 5(B).

(b) (4)

Following that, a Product Deviation Report 09-13-2016 was initiated (see attachment 1B-B). (b) (4) . During the FDA inspection, Issue (b) (4) (IE-00387) was initiated on September 13, 2016 in response to this (b) (4) which then resulted in generation of CAPA CA-02867 on September 19, 2016 (see attachment 1B-D IE-00387, and attachment 1B-E CA-02867). The scope of this CAPA was initially limited to the products in the affected load that were processed through (b) (4) sterilization (b) (4) on (b) (4) However, upon receipt of the FDA-483 observations pertaining to deficiencies in this (b) (4) sterilization validation, Zimmer Biomet incorporated FDA Observations 1(B) and 3(C) into the scope, problem statement, and corrective actions for this open CAPA (i.e., CAPA CA-02867).

During the FDA inspection from September 12, 2016 through November 22, 2016, FDA Investigators identified several nonconformances in the current (b) (4) sterilization validation and subsequent (b) (4) requalifications, upon comparison to the current version of (b) (4) for (b) (4) sterilization, as documented in Observation 1(B). In response to these identified deficiencies, all (b) (4) and Sports Medicine products that are sterilized via this (b) (4) sterilization cycle were (b) (4)

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(b) (4)

(b) (4)

(b) (4)

A few Sports Medicine products (b) (4)

(b) (4)

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(b) (4)

(b) (4)

(b) (4) fractional
cycles were completed with (b) (4) gas dwell times of (b) (4) . (b) (4)

preparation is
detailed in Work Instruction WIG0063 (see attachment 1B-M WIG0063). (b) (4)

(b) (4)

(b) (4)

(b) (4)

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(b) (4) and HHED/HHE evaluations completed for the products in (b) (4) sterilization validation (Validation #79). Sports Medicine devices designated "(b) (4) in Table 1 below represent all (b) (4)

The Sports Medicine (b) (4) (b) (4) (b) (4)

(b) (4) .

Table 1 – (b) (4)

Product Group	(b) (4)	(b) (4)	HHED/HHE
(b) (4)	(b) (4)		

During the recent FDA inspection of the Zimmer Biomet Warsaw North Campus facility, several non-conformances related to (b) (4) were identified in the initial (b) (4) sterilization validation and subsequent (b) (4) requalifications (b) (4) . Zimmer Biomet is committed to performing a fully compliant (b) (4) sterilization validation for all affected (b) (4) devices which will be completed as part of CAPA CA-02867. A fully compliant (b) (4) sterilization validation has already been completed for Sports Medicine devices as part of Preventive Action PA-0539. (b) (4) In the interim, Zimmer Biomet will continue to produce and sterilize (b) (4) and Sports Medicine devices using the current (b) (4) sterilization cycle provided that a SAL of (b) (4) is consistently achieved.

As previously mentioned, CAPA CA-02867 was initially created in response to a (b) (4) during a routine (b) (4) sterilization cycle. This CAPA is currently in the Investigation

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Phase and will be used to perform a comprehensive root cause analysis for all of the deficiencies to (b) (4) that have been identified, including those cited in the examples in Observation 1(B). This CAPA will also be used to document the creation of a fully compliant (b) (4) sterilization validation for all (b) (4) products. In addition, internal procedures, forms, and change controls will be implemented as appropriate to ensure that compliance to the standard is properly maintained. Completed Actions and Planned Actions for this CAPA are documented in the tables below.

Completed Actions:

No.	Action	Completion Date
1B-1	Opened IE-00387 to investigate the (b) (4) result for Load (b) (4) (see attachment 1B-D).	September 13, 2016
1B-2	Confirmed all products from (b) (4) (b) (4)) remained in quarantine status (See attachment 1B-B Product Deviation Report 09-13-2016).	September 14, 2016
1B-3	Initiated CAPA CA-02867 to address the (b) (4) result for (b) (4) (see attachment 1B-E).	September 19, 2016
1B-4	(b) (4) all in-house finished (b) (4) and Sports Medicine products that were sterilized by the (b) (4) Cycle (see attachment 1B-F).	September 20, 2016
1B-5	(b) (4)	September 28, 2016
1B-6	(b) (4) (4) .	(b) (4)
1B-7	(b) (4) for all WIP (see attachment 1B-G).	October 12, 2016
1B-8	(b) (4)	October 27, 2016
1B-9	Initiated Health Hazard Evaluation Determination ("HHED") 12-2016-28 to assess the potential product safety impact of the gaps in the (b) (4) sterilization validation. (see attachment 1B-O).	December 13, 2016

1B-10	Completed (b) (4) , representative (b) (4) simulant, and multiple Sports Medicine products (see attachment 1B-P).	December 14, 2016

Planned Actions:

No.	Action	Completion Date
1B-11	Completion of the comprehensive (b) (4) study and HHE.	(b) (4)
1B-12	Review the documentation from the original 2003 (b) (4) sterilization validation (Validation #79), review the (b) (4) standard that was in place in 2003, and perform a comparison of the two to identify all gaps.	(b) (4)
1B-13	Review all subsequent (b) (4) requalifications for gaps to (b) (4) .	(b) (4)
1B-14	Review internal procedure for (b) (4) sterilization validation that was in place in 2003 to determine if this procedure was in alignment with (b) (4) (b) (4) and if it contained sufficient instructions for conducting an (b) (4) sterilization validation.	(b) (4)
1B-15	(b) (4)	(b) (4)
1B-16	Evaluate all legacy adoption reports for compliance to (b) (4) . Evaluate all non-adopted and poorly adopted products for (b) (4) sterilization compatibility. Contain any products that are not suitable compatible with (b) (4) sterilization.	(b) (4)
1B-17	Review product adoption procedures and report templates and evaluate compliance to the standards.	(b) (4)
1B-18	Evaluate the change control process/procedures to determine if sufficient gatekeeping mechanisms are in place to ensure that product sterility is evaluated in response to: new product introduction, process/product/packaging changes, and changes to the standards governing (b) (4) sterilization.	(b) (4)
1B-19	Evaluate the qualifications of individuals that were previously responsible for (b) (4) sterilization validations, establishing sterile product families, and performing sterile product adoptions to determine if they possessed the knowledge, experience, and training to perform these activities.	(b) (4)

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1B-20	Complete Root Cause analysis	(b) (4)
1B-21	Complete CAPA CA-02978 Investigation (Root Cause/Action Plan) Phase	(b) (4)
1B-22	Perform sufficient (b) (4) studies using current packaging configuration ((b) (4)) to establish comparative resistance relationship between the (b) (4) (b) (4)	(b) (4)
1B-23	Perform full (b) (4) validation with current packaging configuration ((b) (4)) and current sterilization cycle parameters using a "(b) (4)	(b) (4)
1B-24	Complete CA-02978 Implementation Phase.	Target completion date to be reported in a future update
1B-25	Verify effectiveness of CA-02978 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation 1(C)

D. For terminally sterilized devices, validations of sealing machines and associated tools/dies do not provide objective evidence that sealed packaging will consistently meet acceptance criteria with a high degree of assurance. For example:

(b) (4)

Following the FDA inspection, the findings contained in Observation 1(C)(i) regarding the validations for sealers performed . In addition, on September 14, 2016, Zimmer Biomet initiated CAPA CA-02850 to address the findings contained in Observation 1(C)(ii) regarding the installation qualification of sealers. CAPA CA-02380 is discussed below in connection of Observation 1(C)(i).

FDA Observation 1(C)(i)

i. Your firm's Package System Validation Corporate Biomet Procedure, CP1516 Rev. 1 effective 12/17/2010, references conformance to EN 868-5:2009, which (b) (4) **however, all sealer validations performed from 12/17/2010 to 04/07/2016 have not complied with this standard from. For example:**

a. Operational Qualifications and Performance Qualifications performed for sealers and dies do not consistently include verification of seal integrity in accordance with sections 5.3.2 (Operational Qualification) and 5.4.2 (Performance Qualification) of the standard. As of 04/07/2016, your firm implemented (b) (4) **testing, but you have not completed assessment and remediation of all sealer and die validations performed before this date. Your subject matter experts (SMEs) stated that prior to this date, you neither had the capabilities on site nor contacted third parties to perform this testing during equipment/tool validations. Instead, your firm continues to utilize Sterile & Non-Sterile Package Inspect criteria, i00051 version 97 effective 10/28/2015, which includes the following measurement method:** (b) (4)

(b) (4) as well as seal strength testing in the form of peel tests and burst tests.

b. Performance Qualifications are not consistently performed using actual or simulated product in accordance with section 5.4.2 of the standard. Nine (9) out of nine (9) Performance Qualifications reviewed for sealer numbers and (b) (4) did not utilize actual or simulated product in the runs. For example, the Performance Qualification for die SD011-2.2, packaging configurations did not include the use of actual/simulated product that would present the greatest challenge to the process.

c. Performance Qualifications do not consistently include a minimum of (b) (4) production runs to demonstrate repeatability of the process and reproducibility of the results between different runs in accordance with section 5.4.4 of the standard. Three (3) out of nine (9) reviewed Performance Qualifications pertaining to sealer numbers did not include a minimum of production runs. For example, your firm's Die Validation Testing Report for /Suture Anchor Tray approved 2/22/2010 only utilized (b) (4) lot of units.

d. Performance Qualifications did not consider or include challenges that are expected to be encountered during manufacturing in accordance with section 5.4.3 of the standard. For example, your firm did not consistently:

i. Utilize operators to account for person to person variation. For example, your firm's die validation for /Suture Anchor Tray on sealer approved on 02/22/2010 included .

ii. Include power failures or variations to ensure they would not negatively impact the process. Nine (9) out of nine (9) Performance Qualifications reviewed did not challenge the process with power failure/variation. For example, your firm's Performance Qualification for sealer , die ID #(b) (4) approved on 04/28/2016 contains no objective evidence that power interruptions/variation occurred during sealing of the validation units. This practice of challenging the process with

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power failure/variation also conflicts with your firm's Special Process Validation—Sterile Package Sealers procedure, QP0055 Rev. 8 effective 04/07/2016 which states in sections 3.3.2 (b) (4) [redacted]

Observation 1(C)(i) Investigation and Response:

As stated above, prior to the recent FDA inspection, Zimmer Biomet opened CAPA CA-02380 on March 8, 2016 to address findings related to the packaging sealing process (b) (4) [redacted] (see attachment 1Ci-A, *CAPA CA-02380 CAPA Summary*). During the inspection, FDA Investigators reviewed CP1516, *Package System Validation*, Rev. 1 effective December 27, 2010 (see attachment 1Ci-B, CP1516 *Package System Validation*, Rev. 1), which requires conformance to ISO 11607-2 (Packaging for Terminally Sterilized Medical Devices – Part 2: Validation Requirements for Forming, Sealing and Assembly Processes). The inspection noted that all sealer validations performed from December 17, 2010 through April 7, 2016 (b) (4) [redacted] (see attachment 1Ci-C, QP-0055, *Special Process Validation - Sterile Package Sealers*, Rev. 8) have not complied with ISO 11607-2. Specifically, FDA Observation 1(C)(i) identified issues with previously conducted Operational Qualifications ("OQs") and Performance Qualifications ("PQs") for sealers and the associated dies. (b) (4) [redacted] Following the FDA inspection, the findings contained in Observation 1(C)(i) regarding the validations for sealers performed between December 17, 2010 and April 7, 2016 were added to the existing CAPA CA-2380.

In response to the findings in Observation 1(C), Zimmer Biomet initiated the following quality holds:

- (b) (4) [redacted] as discussed in the cover letter to this response, was first implemented on (b) (4) [redacted]
- [redacted] as discussed in the cover letter to this response, was first (b) (4) [redacted], and (b) (4) [redacted]

- (b) (4) and, therefore, no HHED was initiated.
- *QH* (b) (4)) was first implemented on (b) (4) , and applied to WIP product originally listed on Sterilization (b) (4) was implemented (b) (4)

(b) (4) until the completion of an investigation under the appropriate review process and documented in accordance with INST 13.0.2.3 (see attachment 1Ci-F, (b) (4) Rev 3, effective December 6, 2016).

With respect to distributed product in the field, the Zimmer Biomet HHED 12-2016-056 (see attachment 1Ci-D) also addressed the effect of potential gaps in previous validations of sealers in use at the Warsaw North Campus for the packaging of (b) (4) sterilized devices. During (b) (4) (b) (4) . (b) (4)

While Zimmer Biomet investigates the findings in Observation 1(C)(i), as discussed further below, Zimmer Biomet has implemented interim controls that ensure that the sealers operate in a state of control while corrective actions are implemented. First, Zimmer Biomet initiated (b) (4)) to implement increased process monitoring for packaging sealer (b) (4) which was identified in this, and other observations. Further, on November 15, 2016, Zimmer Biomet initiated interim control IC-014, *Process Validation Interim Control* (see attachment 1-B, IC-014, *Process Validation Interim Control*). IC-014 was used (b) (4) The assessment and remediation of sealer (b) (4) was completed per IC-014 (see attachment 1Ci-I, (b) (4) (b) (4)) and is now undergoing routine (b) (4) testing per (b) (4) (see attachment 1Ci-J, QP-0108, (b) (4) . All remaining (b) (4) sealers (b) (4)

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(b) (4)

Zimmer Biomet will continue investigating the issues identified by FDA regarding the sterile package sealer/die validations at the Warsaw North Campus. As part of this investigation, Zimmer Biomet will review the existing validations of all sealers used at the Warsaw North Campus to ensure that they are appropriate for use. Any gaps identified will be remediated and sealers will be revalidated as necessary. (b) (4) As the investigation proceeds, Zimmer Biomet will identify additional corrective actions necessary to address Observation 1(C)(i) and any other gaps or issues identified through the investigation process

Completed Actions:

No.	Action	Completion Date
1C-1	Implemented (b) (4)).	September 29, 2016
1C-2	Implemented (b) (4)	October 12, 2016
1C-3	Implemented (b) (4)).	October 20, 2016
1C-4	Implemented (b) (4) (b) (4)).	October 27, 2016
1C-5	Assessment and (b) (4) sealer (b) (4) was completed per IC-014 (see attachment 1Ci-I, *Validation Summary Report for* (b) (4)	November 9, 2016
1C-6	Initiated (b) (4)).	November 11, 2016

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1C-7	Implemented IC-014, *Process Validation Interim Control* (*see* attachment 1-B*,* IC-014, *Process Validation Interim Control*).	November 15, 2016
1C-8	Added the Observation 1(C)(i) findings to existing CAPA CA-02380 to address the issues identified in Observation 1(C)(i) regarding validation of packaging sealers. (see attachment (1Ci-A *CAPA CA-02380 CAPA Summary*).	December 14, 2016
1C-9	Completed HHED 12-2016-056 (see attachment 1Ci-D, *HHED 12-2016-056*).	December 17, 2016

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Planned Actions:

No.	Action	Completion Date
1C-10	(b) (4)	(b) (4)
1C-11	Review all sterile packaging sealer validation procedures in to ensure they properly comply with ISO 11607-2, the findings of Observation 1(C)(i), and other applicable standards.	(b) (4)
1C-12	Re-evaluate containment decisions, as required and based on the results of the investigation conducted under CA-02380.	(b) (4)
1C-13	Perform Quality Records Search for previous CAPA actions with regards to sterile package sealing validations	(b) (4)
1C-14	Conduct root cause analysis for CA-02380.	(b) (4)
1C-15	Complete CA-02380 Root Cause / Action Plan Phase.	(b) (4)
1C-16	Develop Implementation and Verification of Effectiveness Plan for CA-02380.	Target completion date to be reported in a future update
1C-17	Complete CA-02380 Implementation Phase.	Target completion date to be reported in a future update
1C-18	Verify effectiveness of CA-02380 and close CAPA.	Target completion date to be reported

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		in a future update

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FDA Observation #1Cii

ii. Installation Qualifications (IQs) do not include predetermined acceptance criteria and/or objective evidence that all input requirements for proper functionality have been met. For example:

a. (b) (4) sealers were installed in cleanrooms despite the user manuals for these sealers indicating they were incompatible with a cleanroom environment. When this was identified in the current inspection, the machine vendor was contacted and they subsequently indicated that the exhaust from the system produces particulates. In the time frame from 06/18/2005 to 02/01/2014, your firm installed (b) (4) argon sealers in clean rooms and did not detect this incompatibility.

b. IQ's identify that a gas or compressed air input has been connected to sealers that require these inputs, but they do not contain objective evidence that the input pressures of these gases meet specified requirements. Six (6) out of six (6) IQ's reviewed did not identify the minimum/maximum pressures for these inputs or contained objective evidence that these requirements were met.

Observation 1(C)(ii) Investigation and Response:

On September 14, 2016, Zimmer Biomet opened CAPA CA-02850 to address the findings in Observation 1(C)(ii) concerning the installation qualification ("IQ") conducted for the (b) (4) (b) (4) sealers in use in the cleanrooms used for packaging of (b) (4) sterilized devices (see attachment 1Cii-A). CA-02850 is in the Investigation (Root Cause/Action Plan) Phase.

As identified by FDA in Observation 1(C)(ii)(a), the user manuals (b) (4) of the (b) (4)(b) (4) (b) (4) . As an immediate correction to Observation 1(C)(ii), (b) (4) for (b) (4) sealers (b) (4) (b) (4) . This action was taken following consultation (b) (4) , through which Zimmer Biomet (b) (4) (b) (4) . (b) (4) sealers (b) (4) were already vented outside of the cleanrooms in which they were installed, so no immediate corrections were needed.

During the inspection, Zimmer Biomet shut down the cleanrooms containing (b) (4) sealers, to allow for requalification of the cleanrooms (b) (4) . Requalification of the cleanrooms was completed under Protocols 280, (b) (4) , and included static and dynamic testing under ISO 14644 (*Cleanrooms and Associated Controlled Environments*) (see attachments 1Cii-C, *Protocol 280*, and 1Cii-D, *Protocol 281*). After the completion of requalification activities, the cleanrooms were released and returned to production based on assessments approved on October 31, 2016 (see attachments 1Cii-E, *1 Cii CA-02850 MEMO_31_OCT_16_CR05*, and 1Cii-F, *1 Cii CA-02850 MEMO_31_OCT_16_CR97*). Both assessments justified use of the cleanrooms based on the five (5) following points:

- The rooms continue to meet ISO Class 8 requirements.
- (b) (4)
- The excursions were addressed through site practices and the rooms were fully sanitized prior to resuming operations.
- There is not a direct correlation between microbial air excursions and product bioburden.
- (b) (4) bioburden and dose audits have been completed successfully without sterility failures.

Two (b) (4) sealers have been removed from production ((b) (4)). Sealer (b) (4) was removed from the cleanroom prior to the FDA Inspection and sealer (b) (4) was removed from the cleanroom due to lack of need for the sealer for production. In order for the sealers to be brought back into the cleanroom the sealers would require appropriate installation qualification, (b) (4) . The remaining (b) (4) sealers ((b) (4)) were returned to production after venting and successful clean room qualification testing (see attached 1Cii-J CA-02850 000813WO, 1Cii-K CA-02850 002693, 1Cii-L CA-02850 00010WO).

(b) (4) (b) (4) . In addition to ensuring proper venting of the sealers, the (b) (4) IQ reports will contain objective evidence that the gas and compressed air inputs to the (b) (4) sealers meet the specified requirements, to address Observation 1(C)(ii)(b). The installation qualifications will be conducted in accordance with the procedures established by Interim Control IC-014, *Process Validation Interim Control*, which is in place while new procedures for process validation (b) (4)

(b) (4), as described in the response to Observation 1. The (b) (4) qualifications for all sterile packaging sealers will have specified gas requirements and objective evidence that demonstrates compliance to those requirements.

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
Zimmer Biomet then completed a Containment Assessment (b) (4) under CAPA CA-02850 to determine whether there was a need to continue (b) (4)). The Containment Assessment determined that (b) (4)
(b) (4) .

With respect to distributed product in the field that had been packaged in a cleanroom using an (b) (4) sealer, Zimmer Biomet opened a Health Hazard Evaluation Determination ("HHED") to evaluate the issue (see attachment 1Cii-H, *HHED #09-2016-089*). The HHED was completed on October 7, 2016 and determined that (b) (4)
(b) (4) (b) (4)
concluded that (b) (4)

Zimmer Biomet intends to continue investigating the issues identified by FDA regarding the IQ process and documentation for (b) (4) sealers used in cleanrooms at the Warsaw North Campus. As part of this investigation, Zimmer Biomet will review all other types of sealers used in cleanrooms at the Warsaw North Campus to ensure that they are appropriate for use in cleanrooms. (b) (4)
(b) (4)
. As the investigation proceeds, Zimmer Biomet will identify additional corrective actions necessary to address Observation

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1(C)(ii) and any other gaps or issues identified through the investigation process. Zimmer Biomet will provide details of and timelines for any such actions in future updates to this response.

Completed Actions:

No.	Action	Completion Date
1Cii-1	Initiated CAPA CA-02850 to address the issues identified in Observation 1(C)(ii) regarding installation qualification of (b) (4) sealers used in cleanrooms for the packaging of (b) (4) sterilized devices (see attachment 1Cii-A).	September 14, 2016
1Cii-2	(b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (see attachment 1Cii-B).	September 14, 2016
1Cii-3	(b) (4) and that had been packaged using one of the cleanroom sealers (see attachment 1A-B).	September 29, 2016
1Cii-4	Developed Protocols 280, (b) (4)), for the requalification of cleanrooms (see attachments 1Cii-C and 1Cii-D).	October 05, 2016
1Cii-5	Opened HHED # 09-2016-089 to evaluate the issue identified in Observation 1(C)(ii) regarding (b) (4) sealers used in cleanrooms (see attachment 1Cii-H).	October 07, 2016
1Cii-6	Implemented (b) (4) using one of the cleanroom sealers (see attachment 1B-G).	October 16, 2016
1Cii-7	(b) (4) under CAPA CA-02850 to determine (b) (4) (b) (4) sealers (see attachment 1C-I).	October 20, 2016
1Cii-8	Initiated and completed HHE 2016-214 to make a field action decision for Observation 1(C)(ii) (see attachment 1Cii-I).	December 15, 2016
1Cii-9	Completed correction/containment phase of CA-02850	December 16, 2016

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Planned Actions:

No.	Action	Completion Date
1Cii-10	Perform a review of sealer validations per SOP 9.4.17, *Process Validation Triage Review*, documented on form INST 9.4.17.1.	(b) (4)
1Cii-11	Assess existing sealing equipment currently in use to determine which equipment to validate and which equipment should be replaced.	(b) (4)
1Cii-12	Verify closure of cleanroom qualification reports.	(b) (4)
1Cii-13	Review manufacturer and internal specification for (b) (4) sealers (b) (4)	(b) (4)
1Cii-14	Review all other sealers used in cleanrooms at Warsaw North Campus to determine whether they are appropriate for use in cleanrooms and have defined gas qualification requirements and objective evidence of meeting those requirements.	(b) (4)
1Cii-15	Reassess the need for containment actions, based on the results of the review of other sealers used in cleanrooms at the Warsaw North Campus.	(b) (4)
1Cii-16	(b) (4)	(b) (4)
1Cii-17	Review current IQ and PM documentation for the (b) (4) sealers to determine the installation qualification differences, if any, between the (b) (4) sealers.	(b) (4)
1Cii-18	Perform a Quality Record Search Analysis ("QRSA") for previous CAPA actions concerning environmental controls and packaging sealers.	(b) (4)
1Cii-19	Complete requalification of cleanrooms according to Protocols 280 and 281.	(b) (4)
1Cii-20	Conduct root cause analysis for CA-02850.	(b) (4)
1Cii-21	Complete Investigation (Root Cause/Action Plan) Phase of CA-02850	(b) (4)
1Cii-22	Complete CA-02850 Implementation Phase.	Target completion date to be reported in a future update
1Cii-23	Verify effectiveness of CA-02850 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #1D

E. Your firm's validations for the (b) (4) Water Systems in (b) (4) do not provide adequate assurance that these systems will consistently process water that will meet specifications. These (b) (4) systems supply process water to all processes and equipment with a water input (e.g. (b) (4) cleaners, etc.). For example:

i. Your firm's (b) (4) Water System Validation - (b) (4) Water System approved on 09/08/2015 is inadequate in that:

a. Validation protocols and activities were inadequately reviewed and approved. Detailed review of this validation revealed that your firm does not have a completed validation for the water provided by the (b) (4) Water System. For example,

1. Your firm changed the protocol from Rev. I to Rev. 2 on 04/22/2015 to address changes made to the water system distribution loop during the validation activities, but these changes were not reviewed and approved prior to implementation. Specifically:

a. There is no documentation to show that the original baseline data was re-run, evaluated, and approved after the distribution loop supply line diameter (b) (4) . Section 9.6 of Rev. 2 of the protocol states "(b) (4) The approval pages Rev. 2 of the protocol are lined out and identified as N/ A

2. The validation report was signed and approved on 09/08/2015 even though data gathering activities were not completed until (b) (4) months after the approval date. Section 7.1 of the Process Water System Operational Qualification/Performance Qualification (OQ/PQ) Protocol, Protocol 204

Rev. 1 requires that the sampling plan include (b) (4) Review of the validation report and corresponding objective evidence revealed that only (b) (4) months of (b) (4) testing was performed and analyzed in the report. Further discussions with firm management revealed that data collection activities did not resume until 12/03/2015 and did not conclude until 06/02/2016. As of 10/14/2016, your firm has not organized and evaluated this data to determine if acceptance criteria had been met.(b) (4) Water supplied from the system has direct contact with (b) (4) unique device part numbers through either final cleaning operations or (b) (4) operations for several product families including (b) (4) Water supplied from the (b) (4)System is also used in the mixing of (b) (4) that is used as a sanitizer for work surfaces in all environmentally controlled areas. As such, this water has indirect contact with all sterile products packaged in (b) (4) From 07/01/2014 to 09/09/2016, your firm has manufactured and distributed at least(b) (4) devices that have been processed through cleanrooms in (b) (4)

b. Acceptance criteria were not adequately established in a manner that allows for objective assessment of the validation activities. Section 10 (Acceptance Criteria) of the OQ/PQ protocol references the USP monograph for purified water and provides the following criteria in a table: Total Organic Carbon (b) (4)mg/L, Conductivity (b) (4)µS/cm at (b) (4)C, Endotoxins "Optional" (b) (4) EU/ml, and Total Heterotrophic Count (b) (4) CFU/ml. However, the section also notes the following:

1. (b) (4)

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2. (b) (4)

These notes and acceptance criteria do not establish objective pass/fail criteria.

c. In comparison of the results of your firm's testing performed during the (b) (4) Water System Validation to the specifications provided in the validation's acceptance criteria table, your firm's (b) (4) sample subgroups occurring from 09/23/2014 to 04/07/2015 showed the following:

1. **Polished Water, defined as (b) (4) Water that has not been introduced to the plant distribution loop, was found to exceed:**
   a. **The Total Organic Carbon specification of (b) (4) mg/L in 28 out of 29 samples.**
   b. **The Conductivity specification of (b) (4) µS/cm at 25°C in 0 out of 29 samples.**
   c. **The Endotoxins specification of (b) (4) EU/ml in 1 out of 29 samples.**
   d. **The Total Heterotrophic Count specification of (b) (4) CFU/ml in 2 out of 29 samples.**

2. **Process Water, defined as (b) (4) Water from the plant distribution loop at the point of use, was found to exceed:**
   a. **The Total Organic Carbon specification of (b) (4) mg/L in 28 out of 29 samples.**
   b. **The Conductivity specification of (b) (4) µS/cm at 25°C in 21 out of 29 samples.**
   c. **The Endotoxins specification of (b) (4) EU/ml 0 out of 29 samples.**
   d. **The Total Heterotrophic Count specification of (b) (4) CFU/ml in 0 out of 29 samples.**

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The Results Assessment section of the water system validation report concluded, in part, (b) (4) The analysis of historical data and the rationale for why the process water is suitable for production processing was not documented. Notably, your firm continued to manufacture product using process water during this time frame and no corrective actions were taken in response to the validation results.

d. The Installation Qualifications (IQs) do not include predetermined acceptance criteria and/or objective evidence that all input requirements for proper functionality have been met. For example, your firm utilizes (b) (4) in several parts of the water system to aid in disinfecting (b) (4) and (b) (4) water. These units have a maximum flow rate of (b) (4) gallons per (b) (4) and maximum operating pressure of (b) (4) psi. Your firm has no objective evidence that those requirements have been met.

ii. Your firm's (b) (4) Water System Validation - Biomet (b) (4) Water System Report approved on 11/29/2007 is inadequate in that:

a. Acceptance criteria were not adequately established in a manner that allows for objective assessment of the validation activities. The Acceptance Criteria section of the report states (b) (4) The following criteria are provided in a table: Total Organic Carbon (b) (4) mg/L, Conductivity (b) (4) µS/cm at (b) (4) °C; pH within (b) (4) (b) (4), Endotoxins (b) (4) EU/ml, and Total (b) (4) CFU/ml. However, the section also notes the following:

1. (b) (4)

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(b) (4)

2. **Note 1 states** (b) (4)

These notes and acceptance criteria do not establish objective pass/fail criteria. Notably, your firm concluded that the validation was successful although your firm's validation report documented the following number of failures out of 27 total samples:

Water Type	Conductivity Failures	Total Organic Carbon Failures	Endotoxin Failures	Total Count Failures
Finished	7	6	0	7
Process	8	0	0	9

b. **During the Main System Performance Qualification (PQ), your firm performed corrective actions in response to a trend in Total Counts, but did not repeat the validation in accordance with the established validation protocol. Note 2 in the Acceptance Criteria section states "In the event that the test samples do not meet the acceptance criteria or a trend is noted, a corrective action plan will be necessary before the validation can continue; once corrective actions have been successfully executed, the validation will need to be repeated." The Total Counts section of the PQ states "The total count levels for the Finished water samples exhibited six (6) spikes above the limit with four (4) of the spikes showing a trend. In response to the trend, the water system was sanitized on two occasions according to Quality Process Procedure QP0023** (b) (4) **Water System Monitoring. The sanitization was effective in stopping the trend with acceptable results." The validation report justified not revalidating because "the corrective actions taken to reduce the Total Count test results is an**

established method for controlling water system microbial levels. Review of QP0023 Revisions 1 and 2 that were effective while the validation was occurring indicates that the (b) (4) systems will be sanitized once (b) (4) .

c. Your firm's (b) (4) Water System Addendum to Validation Report for the Biomet (b) (4) Water System approved on 10/16/2007 included (b) (4) months of additional sample collection to confirm that your firm's baseline was appropriately established, but your firm's validation report did not include an objective comparison of the test results with the acceptance criteria. For example:

1. The results section of the Addendum Report states "***the water system output (Finished Water) is consistent with the baseline; the process water exhibited greater fluctuation, however, this was accounted for in the establishment of Monitoring Limits***-" Review of the Process Water test sample results revealed the following quantities of failures when the 36 samples were compared to the acceptance criteria:

Document	Conductivity Failure	Total Organic Carbon Failures	Endotoxin Failures	Total Count Failures
Addendum	15	11[1]	0	0
Baseline[2]	8	0	0	9

Note[1]: Sample #9 had no documented value at "NA"

Note[2]: Baseline testing consisted of 27 samples

Observation 1D Investigation and Response:

On November 30, 2016, Zimmer Biomet opened CAPA CA-03072 to investigate and address the findings in Observation 1(D) regarding the validation of the (b) (4) and (b) (4) water systems that provide process water to all manufacturing operations within (b) (4) (see attachment 1D-A, *CAPA CA-03072 Summary*). CA-03072 is in the Investigation Phase.

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Zimmer Biomet is committed to re-validating the (b) (4) and (b) (4) water systems at the Warsaw North Campus. Prior to beginning re-validation activities, however, Zimmer Biomet will undertake a complete and thorough review of the current water systems, their capabilities, and the needs of the manufacturing facility. This will be an extensive and time-consuming effort, so Zimmer Biomet has implemented several containment actions and interim controls to ensure that product is not negatively impacted by the gaps in the previous validation of the water system.

First, as explained in the cover letter to this response, during the inspection Zimmer Biomet implemented (b) (4) (b) (4)(b) (4)

Second, (b) (4), Zimmer Biomet completed a Health Hazard Evaluation ("HHE") on December 20, 2016 to assess the potential product safety impact of the gaps in the water system validations identified in Observation 1(D) (see attachment 1D-B, *HHE #2016-307*). In addition, Zimmer Biomet is conducting a (b) (4) of water monitoring data to determine the potential impact, if any, of the gaps in the validations on previously produced product. The (b) (4) review will include an analysis of previously recorded excursions, including those identified in Observations 1(D)(i)(c) and 1(D)(ii)(c) and in Observation 2(A), and have been considered under HHE #2016-307.

(b) (4) will be evaluated per IC 004. IC 004 describes the necessary process monitoring requirements to ensure product cleanliness is maintained to pre-determined Zimmer Biomet requirements for endotoxin, debris, cytotoxicity, and TOC. (see attachment 1D-C, *IC 004, Process Monitoring of Final Cleaning*).

Further, to allow continued manufacturing and cleaning operations at the Warsaw North Campus, Zimmer Biomet implemented Interim Control IC 036 on December 14, 2016 to ensure that product is not adversely impacted by the gaps in the previous water system validation (see attachment 1D-D, *IC 036*). (b) (4) Zimmer Biomet trained appropriate personnel to the requirements of the Interim Control, including associated forms (see attachment 1D-E, *IC 036 Training Records*). IC 036 provides for increased monitoring of the water systems and contains processes for sampling, excursion investigations, and excursion

escalation. Under the increased monitoring requirements, Zimmer Biomet will sample and test both water systems (b) (4) for total organic carbon ("TOC"), endotoxins, conductivity and heterotrophic plate count to acquire adequate baseline data. The systems will then be sanitized and then the systems will be sampled again (b) (4) to identify post sanitization conditions. The post sanitization data will be evaluated to determine the sampling and sanitizing frequency going forward. (b) (4) . Under IC 036, improved reaction to excursions will ensure proper response to, and escalation of, exceeding results. Additionally, greater attention to change control requires prior approval of changes, ensures documentation of the system updates, and evaluates the impact to the system. Zimmer Biomet will continue to monitor water system samples based on the evaluation of the data used to characterize the current status of the water system. (b) (4)

(b) (4)

While IC 036 is in place, Zimmer Biomet will fully investigate the (b) (4) water systems in order to develop an appropriate and effective validation protocol for both systems. This investigation will include the following activities: (1) review of existing validation packages in an effort to understand the baseline capability of the water systems; (2) initiation of sampling and testing of incoming (b) (4) water (which supplies the (b) (4) water systems) to characterize system requirements; (3) development of a new system risk assessment and process failure modes and effects analysis ("pFMEA") for the (b) (4) water systems; (4) definition of actual water quality needed for manufacturing operations; (5) review of relevant SOPs, Instructions, Quality Procedures, and data for the Warsaw North Campus and processes and perform a gap assessment of the documents and records against appropriate regulations and standards.

(b) (4)

Using the results of the investigation actions described above, Zimmer Biomet will develop a validation protocol to re-validate the (b) (4) water systems at the Warsaw North Campus. The complete characterization and revalidation of the (b) (4) water systems in

(b) (4) will proceed under the to-be-developed predefined protocol and will be executed under the revised and improved process validation process being implemented under CA-03121 and discussed in the response to Observation 1. In addition, other system-wide quality system efforts will help ensure that the findings in the Observation do not recur, including the revisions to the change control process being implemented under Observation 14. Performing the re-validation in this manner will address all of the issues identified in the examples in Observation 1(D) regarding the original validation of the water system, as well as any additional gaps identified in the investigation conducted under CA-03072. Specifically:

- Observation 1(D)(i)(a)(1): Recurrence of the finding regarding approval of a validation protocol without consideration and specific approval of a change to the (b) (4) during the validation will be prevented by the revisions to the process validation system occurring under CA-03121 discussed in Observation 1 and the revisions to the change control system occurring under CA-02866 discussed in Observation 14. (b) (4) .
- Observation 1(D)(i)(a)(2) and 1(D)(ii)(c): Recurrence of the finding regarding the approval of a validation report prior to the completion and analysis of (b) (4) data gathering activities will be prevented by the revisions to the process validation system occurring under CA-03121 discussed in Observation 1. Additionally, we will complete this outstanding analysis and use the results as an input to the investigation activities being conducted under CA-03072. Further, with respect to the devices processed through cleanrooms in (b) (4) using water from the (b) (4) system from July 1, 2014 through September 9, 2016, as identified in the Observation, historical data (b) (4) will be evaluated. Zimmer Biomet has completed HHE #2016-307 to determine what, if any, risks are posed by the documented excursions and gaps in the previous validation activities for the (b) (4) water system and the potential impact on the safety of product in the field.
- Observations 1(D)(i)(b) and 1(D)(ii)(a): The extensive investigation activities summarized above and to be conducted under CAPA CA-03072 will ensure that Zimmer Biomet establishes appropriate acceptance criteria with objective pass/fail criteria prior to the revalidation of the (b) (4) water systems at the Warsaw North Campus. Although Zimmer Biomet will determine the appropriate specifications for water systems in IC 036, (b) (4)
- Observation 1(D)(i)(c): Revisions to the process validation system occurring under CA-03121 discussed in Observation 1 will ensure that when the (b) (4) water systems are revalidated, any excursions identified during the validation process will be

appropriately analyzed. (b) (4) With respect to the product manufactured during the time frame identified in the Observation (September 23, 2014 to April 7, 2015) through the (b) (4) water system, Zimmer Biomet has completed HHE #2016-307 to determine what, if any, risks are posed by the excursions documented in the validation for the (b) (4) water system

- Observation 1(D)(i)(d): The revisions to the process validation system occurring under CA-03121 discussed in Observation 1 will prevent recurrence of the observation regarding gaps in the Installation Qualification ("IQ") of (b) (4) and all other components of the water systems, specifically, lack of objective evidence that input requirements for the equipment have been met. In addition, Zimmer Biomet plans to re-conduct the IQs for the water systems.
- Observation 1(D)(ii)(a): see Observation 1(D)(i)(b) above.
- Observation 1(D)(ii)(b): The revisions to the process validation system occurring under CA-03121 discussed in Observation 1 will prevent recurrence of the observation regarding the failure to adhere to the requirements in the validation protocol to repeat the validation following implementation of corrective actions.
- Observation 1(D)(ii)(c): see Observation 1(D)(ii)(c) above.

Finally, as described in HHE 2016-307, Zimmer Biomet is confident that the (b) (4) testing implemented under Interim Control IC 004 ensures that product manufactured, processed, and cleaned at Warsaw North Campus under the current water system meets Zimmer Biomet's requirements for endotoxin, TOC, cytotoxicity, and debris despite the identified gaps in the previously conducted system validation. No product is released for distribution if it fails (b) (4), providing assurance that the water system is operating under a state of control sufficient to permit continued operations while the new validation is pending.

Completed Actions:

No.	Action	Completion Date
1D-1	Implemented (b) (4) to contain (b) (4)	September 29, 2016
1D-2	Initiated CAPA CA-03072 to address the issues identified in Observation 1(D) (see attachment 1D-A).	November 30, 2016
1D-3	Toured Buildings (b) (4) at the Warsaw North Campus and identified potential additional areas for investigation.	December 6, 2016
1D-4	(b) (4)	December 7, 2016

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	(b) (4) (b) (4)	
1D-5	Initiated HHED #12-2016-033 to assess the potential product safety impact of the gaps in the water system validations identified in Observation 1(D) (see attachment 1D-B).	December 14, 2016
1D-6	Implemented Interim Control IC 036 for increased monitoring of water systems and to govern sampling, excursion investigations, excursion escalation, and change control (see attachment 1D-D)	December 14, 2016
1D-7	Trained appropriate personnel to the requirements of the IC 036, (see attachment 1D-E).	December 16, 2016

Planned Actions:

No.	Action	Completion Date
1D-8	Sanitize the (b) (4) water systems, per IC 036, (b) (4)	(b) (4)
1D-9	Review historical data (b) (4) .	(b) (4)
1D-10	Review existing validation packages in an effort to understand the baseline capability of the water systems.	(b) (4)
1D-11	Complete the analysis of additional data gathered in the original validation of the water system and identified in Observation 1(D)(i)(a)(2).	(b) (4)
1D-12	Initiate sampling and testing of incoming (b) (4) water (which supplies the (b) (4) water systems) to characterize system requirements.	(b) (4)
1D-13	Perform new system risk assessment and process failure modes and effects analysis ("pFMEA") for the (b) (4) (b) (4) water systems.	(b) (4)
1D-14	Conduct a (b) (4) review of (b) (4) of water monitoring data to determine the potential impact, if any, on previously produced product and analyze previously recorded excursions.	(b) (4)
1D-15	Define actual water quality needed for manufacturing operations.	(b) (4)

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1D-16	Review relevant SOPs, Instructions, Quality Procedures, and data for the Warsaw North Campus and processes and perform a gap assessment of the documents and records against appropriate regulations and standards.	(b) (4)
1D-17	Complete CA-03072 Root Cause / Action Plan Phase	(b) (4)
1D-18	Evaluate post-sanitization data to determine the sampling frequency going forward	(b) (4)
1D-19	Investigate need for and feasibility of additional interim controls for the (b) (4) water systems.	Target completion date to be reported in a future update
1D-20	Continue to monitor the (b) (4) water systems based on the evaluation of the post-sanitization data used to characterize the current status of the water system (per IC 036).	(b) (4) (b) (4)
1D-21	Re-conduct Installation Qualifications for the (b) (4) (b) (4)	Target completion date to be reported in a future update
1D-22	Identify and label sample sites.	Target completion date to be reported in a future update
1D-23	Develop protocol for revalidation of the (b) (4) water systems.	Target completion date to be reported in a future update
1D-24	Revalidate the (b) (4) water systems.	Target completion date to be reported in a future update
1D-25	Complete CA-03072 Implementation Phase.	Target completion date to be reported in a future update
1D-26	Verify effectiveness of CA-03072 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #1(E)

F. Your firm's [redacted] cleaning process for knee femoral implants as governed by work instruction *WIG0035* (Rev. 4, effective 9/19/2011) has not been adequately validated. During the validation of this process (Validation #118, approved 1/21/2010), simulated product (sample CP550157) was [redacted]. The following deficiencies were identified when reviewing Validation #118:

a. The lower specification for detergent concentration was not challenged during the validation. The validation protocol (revised 1/5/2010) and current revision of *Process Engineering Specification 1.15* (Rev. 68, effective 5/10/2016) specify a minimum allowable detergent concentration of [redacted]%. However, a minimum detergent concentration of [redacted]% was used during the validation.

b. The process was not validated with a high degree of assurance to demonstrate that devices meet heavy metal, endotoxin, cytotoxicity, and bioburden test acceptance criteria. Three samples were tested for each of these four requirements during OQ. Statistical rationale was not documented for this sampling plan. During PQ, samples were only subjected to total carbon testing.

c. [redacted]. Your firm was unable to determine when the program change had been made and confirmed that the change was not assessed to determine the need for revalidation.

d. Your firm's Manufacturing Manager explained that the [redacted] tanks are drained and refilled with [redacted] solution at [redacted], however, the number of devices cleaned [redacted] may vary. A maximum number of devices that may be cleaned between tank refills was not established or challenged during the validation.

e. Worst-case conditions were not challenged during the (b) (4) process step and the parameter settings used were not documented. The current revision of *Process Engineering Specification 1.15* (Rev. 68, effective 5/10/2016) defines allowable pressure ranges and orifice sizes to be used when (b) (4). Your firm's Manufacturing Manager said that (b) (4) were run at nominal settings during the validation. *Process Engineering Specification 1.15* also allows for (b) (4) water *or* (b) (4) water to be used with (b) (4). The quality of water used during the validation was not documented.

f. The validation fails to demonstrate that devices which are not required to be (b) (4) during routine production meet the defined requirements (*e.g.*, cytotoxicity). The revision of *Process Engineering Specification 1.15* effective at the time Validation #118 was executed (Rev. 54, effective 12/22/2009 to 2/3/2010) as well as the current revision (Rev. 68, effective 5/10/2016) requires (b) (4) devices to be (b) (4). Your firm's Manufacturing Manager confirmed that (b) (4) metal devices are not required to be (b) (4) and that a separate (b) (4) cleaning validation (b) (4) devices that omits (b) (4) does not exist.

Between 7/1/2014 and 10/13/2016, your firm distributed at least (b) (4) devices that were cleaned via this process.

Observation 1(E) Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03092 (Cleaning Process Validations) to address system-wide issues related to cleaning validations (see attachment 1E-A, *CAPA CA-03092 Summary*). During the recent inspection, FDA identified gaps in legacy Biomet cleaning validations at the Warsaw North Campus. As gaps in the cleaning validations were identified, Zimmer Biomet initiated CAPAs to address them, including:

CAPA	Date Initiated	Cleaning Description	Observation
CAPA CA-02953	October 12, 2016	(b) (4) cleaning process for knee femoral implants	Observation 1(E)
CAPA CA-02936	October 6, 2016	(b) (4) cleaning process for cleaning metal hip, extremities, knee, and trauma devices	Observation 1(F)

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CAPA	Date Initiated	Cleaning Description	Observation
CAPA CA-02863	September 19, 2016	(b) (4) cleaning process for devices made of ultra high molecular weight polyethylene ("UHMWPE")	Observation 1(G)
CAPA CA-02855	September 15, 2016	(b) (4) cleaning process for sports medicine and microfixation devices manufactured from (b) (4) and (b) (4) materials	Observation 1(H)

CAPA CA-03092, which is the parent CAPA for each of the above-listed cleaning-related CAPAs, presently is in the Investigation (Root Cause/Action Plan) Phase. Per CAPA CA-03092, Zimmer Biomet will evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75. Specifically, Zimmer Biomet will ensure that procedures, forms, and work instructions address:

1. Validating processes with a high degree of assurance;
2. Validating processes according to established procedures;
3. Documenting validation activities and results, including the individual approving the validation and the equipment validated;
4. Monitoring and control of process parameters for validated processes; and
5. Review and evaluation of changes or process deviations and resulting revalidation where appropriate.

Upon completion of the evaluation and revision of all cleaning process validation-related procedures, forms, and work instructions, Zimmer Biomet will revalidate all cleaning processes at the Warsaw North Campus. Documentation will be reviewed against revised procedures, forms, and work instructions and remediated so as to conform to those revised procedures, forms, and work instructions.

Furthermore, in assessing cleanliness at the Warsaw North Campus, the standard from the , is the standard that is being used

(b) (4)

* * *

To address the specific issues identified in Observation 1(E) regarding validation of the cleaning process for knee femoral implants at the Warsaw North Campus (specifically Validation #PR118), Zimmer Biomet initiated CAPA CA-02953 on October 26, 2016 (see attachment 1E-D, *CAPA CA-02953 Summary*). CAPA CA-02953 presently is in the Investigation (Root Cause/Action Plan) Phase.

To contain the knee femoral implant products impacted by the cleaning validation issues identified during the inspection, Zimmer Biomet initiated As an additional containment measure, Zimmer Biomet . The table below shows the last implant run before production halt and the first MO run after restart through each of the above Work Centers:

Work Center #	Activity	MO #	Part #	Date	Time	Employee #
)	Halt			10/07/2016		
	Restart			10/27/2016		
	Halt			10/11/2016		
	Restart			10/26/2016		
	Halt			10/13/2016		
	Restart		0	10/27/2016		

The knee femoral implant products) were then subjected to testing); based on such testing, .

The interim controls that Zimmer Biomet adopted included IC 009 (see attachment 1E-H, *IC 009, Revision 1,*), which better documented the

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process and all of its process parameters while also controlling how parts were racked. Going forward, Zimmer Biomet is requiring enhanced process monitoring per IC 004 (see attachment 1D-C, *IC 004, Revision 1, Process Monitoring of Final Cleaning*) of the Warsaw North Campus' [redacted] cleaning process for knee femoral implants [redacted]

Specific corrections related to the observations in Observation 1(E) including the following:

1. To address the process parameter specification ("PPS") issue identified in Observation 1(E)(i), Zimmer Biomet implemented IC 014 (see attachment 1-B, *IC 014, Revision 1,* [redacted]), which employs an approach to validation practices in which all critical PPS are identified, subjected to [redacted] and then challenged in the validation or revalidation. For Observation 1(E)(i), [redacted] In addition, during execution of the revalidation, all PPS used for each operational qualification ("OQ") and performance qualification ("PQ") will be documented so as to provide objective evidence as required by IC 014 (see attachment 1-B). [redacted]

2. To address the statistical rationale issue identified in Observation 1(E)(ii), Zimmer Biomet implemented *CP0972* [redacted] (see attachment 1E-J, *CP0972* [redacted]). The sampling plan in CP0972 uses a [redacted]

3. To address the change control issue identified in Observation 1(E)(iii), Zimmer Biomet will update change control procedures to require appropriate review of process changes to assess their impact on the validation. The updated procedure(s) will require a [redacted] review any proposed changes to a validated process and evaluate the impact of the change, if any, on the validation (see attachment 1E-K, *CAPA CA-03125 Summary*).

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4. To address the PPS issue identified in Observation 1(E)(iv), Zimmer Biomet implemented IC 014 (see attachment 1-B), which employs an approach to validation practices in which all critical PPS are identified, subjected to [redacted], and then challenged in the validation or revalidation. For Observation 1(E)(iv), this will entail identifying the maximum number of devices that may be cleaned between [redacted] and then challenging that number during revalidation of the [redacted] cleaning process for knee femoral implants. In addition, during execution of the revalidation, all PPS used for each OQ and PQ will be documented so as to provide such objective evidence as required by IC 014 (see attachment 1-B). Lastly, per IC 014, section 6.7.2 (see attachment 1-B); [redacted]

5. To address the PPS issue identified in Observation 1(E)(v), Zimmer Biomet implemented IC 014 (see attachment 1-B), which employs an approach to validation practices in which all critical PPS are identified, subjected to [redacted], and then challenged in the validation or revalidation. For Observation 1(E)(v), Zimmer Biomet implemented IC 009 (see attachment 1E-H) and IC 010 (see attachment 1E-L, *IC 010, Revision 1,* [redacted]) which discontinued work center [redacted]

   Zimmer Biomet also will address a concern of Observation 1(E)(v) by documenting the quality of the water used during the revalidation. The Validation Plan (see attachment 1E-M, *ICF 014.9, Revision 3, Validation Plan*) clearly specifies the water requirement, the source document, and the respective validation.

   In addition, during execution of the revalidation, all PPSs used for each OQ and PQ will be documented so as to provide such objective evidence as required by IC 014 (see attachment 1-B). [redacted]

6. To address the worst-case rationale issue identified in Observation 1(E)(vi), Zimmer Biomet will use rules developed [redacted] to identify worst-case scenarios for testing. The [redacted] rules require review of certain product characteristics when making worst-case determinations. [redacted]. For Observation 1(E)(vi), Zimmer Biomet will revalidate the [redacted] cleaning process for knee femoral implants in a manner that addresses whether [redacted] metal devices must be subject to [redacted]. This [redacted] cleaning process will then be validated in a manner that documents that the actual product used presents and equal or greater challenge than the metal devices that are the most difficult to clean. A new [redacted] Cleaning System is being implemented as [redacted] which specifies a product grouping matrix demonstrating such grouping of products to determine a worst-case (see attachment 1E-N, [redacted]*)*.

Pursuant to CAPA CA-02953, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 1(E)(i)-(vi);
2. Develop an implementation plan for CAPA CA-02953; and
3. Develop a verification of effectiveness ("VoE") for CAPA CA-02953.

Pursuant to parent CAPA CA-03092 (Cleaning Process Validations), Zimmer Biomet will conduct a system-wide investigation of its procedures for cleaning process validations that includes the following tasks:

1. Conduct a root-cause analysis of the system-wide cleaning validation issues identified in Observations 1(E) through 1(H);
2. Harmonize validation requirement to implement elements of IC 014;
3. Update the Validation Master Plan (Cleaning Process Validations);
4. Implement interim controls prior to restarting production cells which were halted during the inspection to ensure appropriate controls and provide objective evidence of process controls;
5. Complete [redacted] testing on halted and low-risk products to provide an assessment of containment and resolve product holds;
6. Implement the harmonized cleaning requirements between [redacted]

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7. Evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75;
8. Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of all cleaning process validations;
9. Revalidate all cleaning processes at the Warsaw North Campus;
10. Complete CAPA CA-03092 (Cleaning Process Validations) implementation phase;
11. Verify effectiveness of CAPA CA-03092 (Cleaning Process Validations) and close CAPA.

With respect to the at least (b) (4) devices that were cleaned via the (b) (4) cleaning process for knee femoral implants and then distributed between July 1, 2014, and October 13, 2016, Zimmer Biomet initiated a health hazard evaluation determination ("HHED") on November 15, 2016 (see attachment 1E-O, *HHED 10-2016-038*). The resulting health hazard evaluation ("HHE") was completed (b) (4)

Completed Actions:

No.	Action	Completion Date
1E-1	Implemented *CP0972 Process Validation Sampling Plan* (see attachment 1E-J, *CP0972, Revision 1, Process Validation Sampling Plan*).	January 9, 2013
1E-2	(b) (4)(b) (4) (b) (4)) cited in Observation 13(E).	October 11, 2016
1E-3	Initiated CAPA CA-02953 to address the specific issues identified in Observation 1(E) regarding validation of the (b) (4) cleaning process for knee femoral implants at the Warsaw North Campus (specifically Validation #PR118) (see attachment 1E-D, *CAPA CA-02953 Summary*).	October 12, 2016
1E-4	(b) (4)	October 12, 2016
1E-5	(b) (4) to (b) (4) testing (b) (4) (b) (4) (b) (4), (b) (4)	October 16, 2016

No.	Action	Completion Date
1E-6	Implemented Interim Control IC 004, (b) (4) , to describe the necessary statistically valid process monitoring requirements to ensure product cleanliness is maintained to pre-determined Zimmer Biomet requirements, until processes can be re-validated (see attachment 1D-C, *IC 004, Revision 1,* (b) (4)).	October 20, 2016
1E-7	Implemented Interim Control IC 009, (b) (4) to prescribe necessary manufacturing controls to ensure the effectiveness of the (b) (4) cleaning process until the process has been revalidated (see attachment 1E-H, *IC 009, Revision 1,* (b) (4)).	October 26, 2016
1E-8	(b) (4) Production re-start per IC 009 (see attachment 1E-H).	October 26, 2016
1E-9	Implemented IC 014, which employs an approach to validation practices in which all critical PPS are identified, (b) (4)), and then challenged in the validation or revalidation (see attachment 1-B, *IC 014, Revision 1,* (b) (4)).	November 1, 2016
1E-10	Adopted rules developed at the (b) (4) to identify worst-case scenarios for testing (b) (4)	December 8, 2016
1E-11	Initiated an effort to harmonize the (b) (4) cleaning processes at the (b) (4) with the (b) (4) cleaning processes (b) (4)	November 8, 2016
1E-12	Initiated HHED 10-2016-038 (see attachment 1E-O, *HHED 10-2016-038*).	November 15, 2016
1E-13	Initiated CAPA CA-03092 (Cleaning Process Validations) to address system-wide issues related to cleaning validations (see attachment 1E-A, *CAPA CA-03092 Summary*).	December 1, 2016
1E-14	Initiated HHE 2016-258 (see attachment 1E-P, HHE 2016-258)	December 16, 2016

Planned Actions:

No.	Action	Completion Date
1E-15	Complete efforts to harmonize (b) (4) cleaning processes at the (b) (4) with the (b) (4) cleaning processes at the (b) (4) .	(b) (4)
1E-16	Update Validation Master Plan.	(b) (4)

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No.	Action	Completion Date
1E-17	Implement interim controls prior to production cell restarts to ensure appropriate controls and provide objective evidence of process controls.	(b) (4)
1E-18	Complete (b) (4) testing on halted and low-risk products to provide assessment of containment so as to resolve products on hold.	(b) (4)
1E-19	Complete CAPA CA-03092 (Cleaning Process Validations) Root Cause / Action Plan phase.	(b) (4)
1E-20	Per CAPA CA-03092, evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75.	Target completion date to be reported in a future update
1E-21	Per CAPA CA-03092, revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of all cleaning process validations.	Target completion date to be reported in a future update
1E-22	Per CAPA CA-03092, revalidate all cleaning processes at the Warsaw North Campus.	Target completion date to be reported in a future update
1E-23	Complete CAPA CA-03092 (Cleaning Process Validations) implementation phase.	Target completion date to be reported in a future update
1E-24	Verify effectiveness of CAPA CA-03092 (Cleaning Process Validations) and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #1(F)

G. Your firm's manual cleaning process used to clean metal hip, extremities, knee, trauma, microfixation, and sports medicine devices as governed by work instruction *WIGO151* (Rev. I, effective 4/21/2015) has not been adequately validated. During the validation of this process (Validation #141, approved 12/7/2010), simulated product (sample CP550157) was subjected to the following process flow: [redacted] The following deficiencies were identified when reviewing Validation #141:

a. Justification that the simulated product used during the validation presents an equal or greater challenge than the metal device(s) that is/are most difficult to clean by this process was not documented.

b. The validation protocol (approved 11/19/20 10) states that [redacted] Such "established methods" had not been adequately documented at the time of the validation. Your firm's Manufacturing Manager stated that localized cleaning is currently controlled by work instruction *WIGO151* (Rev. 1, effective 4/21/2015), which describes how to use "approved chemicals" (*e.g.*, [redacted] solvent and [redacted]) with brushes, cotton swabs, wipes, pipe cleaners, and other materials to manually clean various features of devices (*e.g.*, porous surfaces, polished surfaces, holes, threads, grooves, slots, etc.). *WIG0151* was initially released on 4/21/2015 and thus did not exist at the time of the validation. The only process specification referenced by the validation is *Process Engineering Specification 1.15* (Rev. 56, effective 6/10/2010 to 12/6/2010), which lists approved chemicals and materials but does not define how or when they are to be used when cleaning various device features.

c. The chemical(s) used during the localized cleaning process step were not documented. The current revision of *WIG0151* (Rev. 1, effective 4/21/2015) instructs operators to use "approved chemicals" per *Process Engineering Specification 1.15* when manually cleaning metal devices. The current revision of *Process Engineering Specification 1.15* (Rev. 68, effective 5/10/2016) lists [redacted] approved chemicals which may be used.

d. **Worst-case conditions were not challenged during the (b) (4) process step and the parameter settings used were not documented. The current revision of *Process Engineering Specification 1.15* (Rev. 68, effective 5/10/2016) defines allowable pressure ranges and orifice sizes to be used when (b) (4). Your firm's Manufacturing Manager said that (b) (4) were run at nominal settings during the validation. *Process Engineering Specification 1.15* also allows for (b) (4) water *or* (b) (4) water to be used with (b) (4). The quality of water used during the validation was not documented.**

e. **The validation fails to demonstrate that devices which are not required to be (b) (4) during routine production meet the defined requirements *(e.g.,* cytotoxicity). The revision of *Process Engineering Specification 1.15* referenced by the validation (Rev. 56, effective 6/10/2010 to 12/6/2010) as well as the current revision (Rev. 68, effective 5/10/2016) requires (b) (4) devices to be (b) (4). Your firm's Manufacturing Manager confirmed that (b) (4) metal devices are not required to be power washed and that a separate manual cleaning validation that omits (b) (4) does not exist.**

f. ***WIG0151* (Rev. 1. effective 4/21/2015) allows the use of a (b) (4) cleaner and/or (b) (4) cleaner to remove "heavy debris" from devices. The revision of *Process Engineering Specification 1.15* referenced by the validation (Rev. 56, effective 6/10/2010 to 12/6/2010) makes no reference to these pieces of equipment. Your firm's Manufacturing Manager stated that these pieces of equipment were not in use at the time of the validation.**

g. **Several parts of *WIG0151* (Rev. I, effective 4/21/2015) instruct operators to assess device cleanliness by visual inspection. Your firm's Director of Quality Assurance confirmed that such visual inspection methods have been validated to demonstrate repeatable and reproducible results. For example:**

Section of WIG0151	Requirement
(b) (4)	(b) (4)
(b) (4)	(b) (4)

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

Between 7/1/2014 and 10/13/2016, your firm distributed at least devices that were cleaned via this process.

Observation 1(F) Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03092 (Cleaning Process Validations) to address system-wide issues related to cleaning validations (see attachment 1E-A, *CAPA CA-03092 Summary*). During the recent inspection, FDA identified gaps in legacy Biomet cleaning validations at the Warsaw North Campus. As gaps in the cleaning validations were identified, Zimmer Biomet initiated CAPAs to address them, including:

CAPA	Date Initiated	Cleaning Description	Observation
CAPA CA-02953	October 12, 2016	(b) (4) cleaning process for knee femoral implants	Observation 1(E)
CAPA CA-02936	October 6, 2016	(b) (4) cleaning process for cleaning metal hip, extremities, knee, and trauma devices	Observation 1(F)
CAPA CA-02863	September 19, 2016	(b) (4) cleaning process for devices made of ultra high molecular weight polyethylene ("UHMWPE")	Observation 1(G)
CAPA CA-02855	September 15, 2016	(b) (4) cleaning process for sports medicine and microfixation devices manufactured from (b) (4) materials	Observation 1(H)

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CAPA CA-03092, which is the parent CAPA for each of the above-listed cleaning-related CAPAs, presently is in the Investigation (Root Cause/Action Plan) Phase. Per CAPA CA-03092, Zimmer Biomet will evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75. Specifically, Zimmer Biomet will ensure that procedures, forms, and work instructions address:

1. Validating processes with a high degree of assurance;
2. Validating processes according to established procedures;
3. Documenting validation activities and results, including the individual approving the validation and the equipment validated;
4. Monitoring and control of process parameters for validated processes; and
5. Review and evaluation of changes or process deviations and resulting revalidation where appropriate.

Upon completion of the evaluation and revision of all cleaning process validation-related procedures, forms, and work instructions, Zimmer Biomet will revalidate all cleaning processes at the Warsaw North Campus. Documentation will be reviewed against revised procedures, forms, and work instructions and be remediated so as to conform to those revised procedures, forms, and work instructions. Furthermore, in assessing cleanliness at the Warsaw North Campus, the standard from the , is the standard that is being used .

* * *

To address the specific issues identified in Observation 1(F) regarding validation of the cleaning process used to clean metal hip, extremities, knee, and trauma devices at the Warsaw North Campus (specifically Validation #PR141), Zimmer Biomet initiated CAPA CA-02936 on October 6, 2016 (see attachment 1E-A, *CAPA CA-02936 Summary*). CAPA CA-02936 presently is in the Investigation (Root Cause/Action Plan) Phase. Although the CAPA investigation is not complete, it appears that the root causes cleaning process used to clean metal hip, extremities, knee, and trauma devices (i.e., Validation

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#PR141

To contain the metal hip, extremities, knee, and trauma devices impacted by the cleaning validation issues identified during the inspection, Zimmer Biomet initiated . As an additional containment measure, Zimmer Biomet converted cleaning operations at the work centers associated with the cleaning validation (Validation #PR141) which are from final to clean work centers and the associated Manufacturing Orders (MO) are routed either to work centers for final cleaning which are remediated through interim controls and enhanced process monitoring. The work centers associated with the The table below shows the first implant ( ) MO run after restart through each of the above final clean work centers:

Work Center #	Activity	MO #	Part #	Date	Time	Employee #
	Restart with IC 017			11/03/2016		
	Restart with IC 017			10/31/2016		
	Restart with IC 009			10/27/2016		
)	Restart with IC 009			10/26/2016		
)	Restart with IC 009			10/27/2016		

(b) (4)
(b) (4) (b) (4)
The associated work centers shall continue production under

interim controls and enhanced process monitoring. These cleaning lines serve devices and small components that . The lines have no signals of cleanliness issues through process monitoring, and do not clean products. Based on that testing, the

CAPA Cleaning Assessment	Laboratory Test	Result	Date
(b) (4)	(b) (4)	(b) (4)	
(b) (4))	(b) (4)	(b) (4)	(b) (4)

(b) (4)

CAPA Cleaning Assessment	Laboratory Test	Result	Date
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)			
(b) (4))			

Zimmer Biomet will resolve these through CAPA CA-02936 investigation.

The interim controls that Zimmer Biomet adopted included IC 004 (see attachment 1D-C, *IC 004, Revision 1, Process Monitoring of Final Cleaning*), which describes the necessary process monitoring requirements to ensure product cleanliness is maintained to pre-determined Zimmer Biomet requirements, until processes can be re-validated, IC 009 (see attachment 1E-H, *IC 009, Revision 1,*), which prescribes the necessary manufacturing controls to ensure the effectiveness of the final cleaning process until the process has been revalidated, IC 014 (see attachment 1-B, *IC 014, Revision 1, Process Validations Interim Control*), which establishes the procedure needed to conduct validations while new procedures are being established on the Warsaw North Campus, and IC 017 (see attachment 1F-C, *IC 017, Revision 1,*), which prescribes the necessary manufacturing controls to ensure the effectiveness of the cleaning process until the process has been revalidated. Going forward, Zimmer Biomet is requiring enhanced process monitoring of the Warsaw North Campus' final cleaning process used to clean metal hip, extremities, knee, and trauma devices to cleaning

standards using IC 004 until the process is revalidated. Specific corrections related to the observations in Observation 1(F) including the following:

1. To address the worst case rationale issue identified in Observation 1(F)(i), Zimmer Biomet will use [redacted]. For Observation 1(F)(i), Zimmer Biomet will convert the [redacted] cleaning process used to clean metal hip, extremities, knee, and trauma devices to [redacted] cleaning which will be followed or replaced [redacted]. This final cleaning process will then be validated in a manner that documents that the actual product used presents and equal or greater challenge than the metal devices that are the most difficult to clean. A new [redacted] Cleaning System is being implemented [redacted] using IC 014 which specifies a product grouping matrix demonstrating such grouping of products to determine a worst-case (see attachment 1F-D, [redacted]).

2. To address the manufacturing materials issue identified in Observation 1(F)(ii), Zimmer Biomet implemented a procedure that requires (a) that manufacturing materials used in production cells be documented and (b) that a formal request must be submitted in order to introduce new manufacturing materials into the production cell (see attachment 1F-E, *SOP 9.0.1, Revision 1, Manufacturing Materials (Production Supplies)*, and attachment 1F-F, *MM Master 01, Revision 1, Manufacturing Materials—Master List*). For Observation 1(F)(ii), Zimmer Biomet will convert the [redacted] cleaning process used to clean metal hip, extremities, knee, and trauma devices to [redacted] cleaning which will be followed or replaced by [redacted] final cleaning. This final cleaning process will then be validated so that approved chemicals and materials approved for use in the cleaning process are part of the validation.

3. To address the manufacturing materials issue identified in Observation 1(F)(iii), Zimmer Biomet implemented a procedure that requires (a) that manufacturing materials used in production cells be documented and (b) that a formal request must be submitted in order to introduce new manufacturing materials into the production cell (see attachment 1F-E, and attachment 1F-F). For Observation 1(F)(iii), Zimmer Biomet will convert the [redacted] cleaning process used to clean metal hip, extremities, knee, and trauma devices to [redacted] cleaning which will be followed or replaced by [redacted]

(b) (4) final cleaning. This final cleaning process will then be validated so that chemicals used during the cleaning process steps are documented.

4. To address the process parameter specification ("PPS") issue identified in Observation 1(F)(iv), Zimmer Biomet implemented IC 014 which employs an approach to validation practices in which all critical PPS are identified, subjected to and then challenged in the validation or revalidation. For Observation 1(F)(iv), this will entail o . For example, see section 16.7 " " of IC 014 Appendix 01, Process Validation General Requirements (see attachment 1-B).

5. To address the worst case rationale issue identified in Observation 1(F)(v), Zimmer Biomet will use rules developed at the to identify worst-case scenarios for testing. . For Observation 1(F)(v), Zimmer Biomet will convert the cleaning process used to clean metal hip, extremities, knee, and trauma devices to cleaning which will be followed or replaced by final cleaning. This final cleaning process will then be validated in a manner that accurately identifies .

6. To address the worst case rationale issue identified in Observation 1(F)(vi), Zimmer Biomet will use rules developed at the to identify worst-case scenarios for testing. . For Observation 1(F)(vi), Zimmer Biomet will convert the cleaning process used to clean metal hip, extremities, knee, and

trauma devices to [redacted] cleaning which will be followed or replaced by an [redacted] final cleaning. This final cleaning process will then be validated in a manner to remove "heavy debris" as well as all other final cleanliness requirements of Zimmer Biomet implants.

7. To address the product requirements issue identified in Observation 1(F)(vii), Zimmer Biomet is implementing QP 0114 (see attachment 1F-G, *QP 0114, Revision 1,* [redacted]), which defines final cleanliness requirements of Zimmer Biomet implants through testing of residual materials and bacterial endotoxin. For Observation 1(F)(vii), Zimmer Biomet will convert the [redacted] cleaning process used to clean metal hip, extremities, knee, and trauma devices to [redacted] cleaning which will be followed or replaced by [redacted] final cleaning. This final cleaning process will then be validated in compliance with appropriate product requirements and test method validations.

Pursuant to CAPA CA-02936, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 1(F)(i)-(vii);
2. Develop an implementation plan for CAPA CA-02936; and
3. Develop a verification of effectiveness ("VoE") for CAPA CA-02936;

Pursuant to parent CAPA CA-03092 (Cleaning Process Validations), Zimmer Biomet will conduct a system-wide investigation of its procedures for cleaning process validations that includes the following tasks:

1. Conduct a root-cause analysis of the system-wide cleaning validation issues identified in Observations 1(E) through 1(H);
2. Harmonize validation requirement to implement elements of IC 014;
3. Update the Validation Master Plan (Cleaning Process Validations);
4. Implement interim controls prior to [redacted] to ensure appropriate controls and provide objective evidence of process controls;
5. Complete [redacted] testing on halted and low-risk products to provide an assessment of containment and resolve product holds;
6. Implement the harmonized cleaning requirements as between the [redacted] and the [redacted] as set forth in [redacted];

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7. Evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75;
8. Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of all cleaning process validations;
9. Revalidate all cleaning processes at the Warsaw North Campus;
10. Complete CAPA CA-03092 (Cleaning Process Validations) implementation phase;
11. Verify effectiveness of CAPA CA-03092 (Cleaning Process Validations) and close CAPA.

With respect to the at least (b) (4) devices that were cleaned via the (b) (4) cleaning process used to clean metal hip, extremities, knee, and trauma devices and then distributed between July 1, 2014, and October 13, 2016, Zimmer Biomet initiated a health hazard evaluation determination ("HHED") on November 15, 2016 (see attachment 1F-H, *HHED 10-2016-037*). The resulting health hazard evaluation ("HHE") was completed on December 18, 2016 (b) (4)

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

(b) (4)

Completed Actions:

No.	Action	Completion Date
1F-1	Initiated CAPA CA-02936 to address the specific issues identified in Observation 1(F) regarding validation of the (b) (4) cleaning process for metal hip, extremities, knee, and trauma devices at the Warsaw North Campus (specifically Validation #PR141) (see attachment 1E-A).	October 6, 2016
1F-2	Implemented Quality Hold 16-068-01 (see attachment 1B-G).	October 12, 2016
1F-3	Converted cleaning operations at the work centers associated with the inadequate cleaning validation (Validation #PR141) cited in Observation 1(F) to (b) (4) clean work centers and (b) (4) at (b) (4) for final cleaning.	October 13, 2016
1F-4	Implemented Interim Control IC 004, *Process Monitoring of Final Cleaning*, to describe the necessary process monitoring requirements to ensure product cleanliness is maintained to pre-determined Zimmer Biomet requirements, until processes can be re-validated (see attachment 1D-C).	October 20, 2016
1F-5	Subjected the metal hip, extremities, knee, and trauma devices (b) (4) (b) (4) (b) (4)	October 24, 2016 to December 2, 2016

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No.	Action	Completion Date
1F-6	Implemented Interim Control IC 009, (b) (4) to prescribe necessary manufacturing controls to ensure the effectiveness of the (b) (4) final cleaning process until the process has been revalidated (see attachment 1E-H, *IC 009, Revision 1,* (b) (4)).	October 26, 2016
1F-7	(b) (4) (b) (4) .	October 26, 2016
1F-8	Implemented Interim Control IC 017, (b) (4) , to prescribe the necessary manufacturing controls to ensure the effectiveness of the (b) (4) final cleaning process until the process has been revalidated (see attachment 1F-C).	October 31, 2016
1F-9	(b) (4) Production re-start.	October 31, 2016
1F-10	Implemented IC 014, *Process Validations Interim Control*, which employs an approach to validation practices in which all critical PPS are identified, subjected to (b) (4)), and then challenged in the validation or revalidation (see attachment 1-B).	November 1, 2016
1F-11	Implemented a procedure that requires (a) that manufacturing materials used in production cells be documented and (b) that a formal request must be submitted in order to introduce new manufacturing materials into the production cell (see attachment 1F-E, and attachment 1F-F).	November 8, 2016
1F-12	Implemented rationale to harmonize the (b) (4) cleaning processes at the (b) (4) with the (b) (4) cleaning processes at the (b) (4) (b) (4)	November 8, 2016
1F-13	Initiated HHED 10-2016-037 (see attachment 1F-H).	November 15, 2016
1F-14	Initiated CAPA CA-03092 (Cleaning Process Validations) to address system-wide issues related to cleaning validations (see attachment 1E-A).	December 1, 2016
1F-15	Adopted rules developed at the (b) (4) (b) (4) to identify worst-case scenarios for testing through (b) (4) Cleaning Process Validation Plan (see attachment 1F-D).	December 8, 2016
1F-16	Implemented QP 0114 to define final cleanliness requirements of Zimmer Biomet implants through testing of residual materials and bacterial endotoxin (see attachment 1F-G).	December 16, 2016
1F-17	Completed HHE 2016-257 (see attachment 1F-I).	December 18, 2016

Planned Actions:

No.	Action	Completion Date
1F-18	Complete efforts to harmonize the (b) (4) cleaning processes at the (b) (4) with the (b) (4) cleaning processes at the (b) (4) (b) (4) as set forth in (b) (4) .	(b) (4)

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No.	Action	Completion Date
1F-19	Update Validation Master Plan (Clean Process Validations).	(b) (4)
1F-20	Implement interim controls prior to production cell restarts to ensure appropriate controls and provide objective evidence of process controls.	(b) (4)
1F-21	Complete (b) (4) testing on halted and low-risk products to provide assessment of containment so as to resolve products on hold.	(b) (4)
1F-22	Complete CAPA CA-03092 (Cleaning Process Validations) Root Cause / Action Plan phase.	(b) (4)
1F-23	Per CAPA CA-03092, evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75.	Target completion date to be reported in a future update
1F-24	Per CAPA CA-03092, revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of all cleaning process validations.	Target completion date to be reported in a future update
1F-25	Per CAPA CA-03092, revalidate all cleaning processes at the Warsaw North Campus.	Target completion date to be reported in a future update
1F-26	Complete CAPA CA-03092 (Cleaning Process Validations) implementation phase.	Target completion date to be reported in a future update
1F-27	Verify effectiveness of CAPA CA-03092 (Cleaning Process Validations) and close CAPA.	Target completion date to be reported in a future update

FDA Observation #1(G)

H. Your firm's manual cleaning process for devices made of ultra-high-molecular-weight polyethylene (UHMWPE) by submersion in a bath of) as governed by work instruction *WIG0150* (Rev. 3, effective 5/5/2016) has not been adequately validated. The following deficiencies were identified when reviewing the validation of this process (Validation #53, approved 12/20/2004):

a. *WIG0150* (Rev. 3, effective 5/4/2016) requires a submersion time of minutes (per *Process Engineering Specification 1.15*). Submersion time was not mentioned in the validation protocol or report. As such, your firm could not provide objective evidence that the worst-case condition of minutes was challenged.

b. While watching the cleaning operation on 9/14/2016, the operator explained that baths are drained and refilled and that there is no limit to the amount of devices that may be placed in the bath . A maximum number of devices that may be cleaned between bath refills was not established or challenged during the validation.

c. 12 devices were tested for bioburden, endotoxin, and cytotoxicity during the validation. Statistical rationale for this sampling plan was not documented.

d. Section A, Step 3 of WIGO150 instructs operators to " after soaking devices in the bath. Your firm could not provide objective evidence that this visual inspection method has been validated to demonstrate repeatable and reproducible results.

Between 7/1/2014 and 10/13/2016, your firm distributed at least devices that were cleaned via this process.

Observation 1(G) Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03092 (Cleaning Process Validations) to address system-wide issues related to cleaning validations (see attachment 1E-A, *CAPA CA-*

03092 Summary). During the recent inspection, FDA identified gaps in legacy Biomet cleaning validations at the Warsaw North Campus. As gaps in the cleaning validations were identified, Zimmer Biomet initiated CAPAs to address them, including:

CAPA	**Date Initiated**	**Cleaning Description**	**Observation**
CAPA CA-02953	October 26, 2016	(b) (4) cleaning process for knee femoral implants	Observation 1(E)
CAPA CA-02936	October 6, 2016	(b) (4) cleaning process for cleaning metal hip, extremities, knee, trauma.	Observation 1(F)
CAPA CA-02863	September 19, 2016	(b) (4) cleaning process for devices made of ultra high molecular weight polyethylene ("UHMWPE")	Observation 1(G)
CAPA CA-02855	September 15, 2016	(b) (4) cleaning process for sports medicine and microfixation devices manufactured from (b) (4) and (b) (4) materials	Observation 1(H)

CAPA CA-03092, which is the parent CAPA for each of the above-listed cleaning-related CAPAs, presently is in the Investigation (Root Cause/Action Plan) Phase. Per CAPA CA-03092, Zimmer Biomet will evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75. Specifically, Zimmer Biomet will ensure that procedures, forms, and work instructions address:

1. Validating processes with a high degree of assurance;
2. Validating processes according to established procedures;
3. Documenting validation activities and results, including the individual approving the validation and the equipment validated;

4. Monitoring and control of process parameters for validated processes; and
5. Review and evaluation of changes or process deviations and resulting revalidation where appropriate.

Upon completion of the evaluation and revision of all cleaning process validation-related procedures, forms, and work instructions, Zimmer Biomet will revalidate all cleaning processes at the Warsaw North Campus. Documentation will be reviewed against revised procedures, forms, and work instructions and be remediated so as to conform to those revised procedures, forms, and work instructions. Furthermore, in assessing cleanliness at the Warsaw North Campus, the standard from the , , is the standard that is being used

* * *

To address the specific issues identified in Observation 1(G) regarding validation of the manual cleaning process for devices made of ultra high molecular weight polyethylene ("UHMWPE") at the Warsaw North Campus (specifically Validation #PR53), Zimmer Biomet initiated CAPA CA-02863 on September 19, 2016 (see attachment 1G-A, *CAPA CA-02863 Summary*). CAPA CA-02863 presently is in the Investigation (Root Cause/Action Plan) Phase. .

Containment of the UHMWPE devices impacted by the cleaning validation (Validation #PR53) issues identified during the inspection was already in place under Quality Hold , for sterilization validation issues, while testing was conducted. The testing indicated the devices were conforming to the requirements of and no additional cleaning related hold was initiated. As an additional containment measure, (b) (4)) (b) (4) (b) (4) (b) (4)

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

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	Halt			10/11/2016		
	Restart			10/20/2016		

The interim controls that Zimmer Biomet adopted for Ultra High Molecular Weight Polyethylene (UHMWPE) Final Cleaning include (b) (4) which details the critical process parameters and requires documentation of these steps in the DHR, IC-030 (see attachment 1G-D, *IC 030, Revision 1,*), which details , and IC-031 (see attachment 1G-E, *IC 031, Revision 1,*), which details . Going forward, Zimmer Biomet is requiring enhanced process monitoring of the Warsaw North Campus' cleaning process for UHMWPE devices to cleaning standards until the process is revalidated. Process monitoring is defined in IC 004 (see attachment 1D-C, *IC 004, Revision 1,* Specific corrections related to the observations in Observation 1(G) including the following:

1. To address the process parameter specification ("PPS") issue identified in Observation 1(G)(i), Zimmer Biomet implemented IC-014 (see attachment 1G-K, *IC-014, Revision 1,*), which employs an approach to validation practices in which all critical PPS are identified, subjected to and then challenged in the validation or revalidation. For Observation 1(G)(i), this will entail determining whether In addition, during execution of the revalidation, all PPS used for each operational qualification ("OQ") and performance qualification ("PQ") will be documented so as to provide objective evidence. All PPS shall be listed in the Process Failure Mode Effects Analysis ("PFMEA") for risk analysis to patients.

2. To address the PPS issue identified in Observation 1(G)(ii), Zimmer Biomet implemented IC-014 (see attachment 1G-K, *IC-014, Revision 1,*),

which employs an approach to validation practices in which all critical PPS are identified, subjected to [redacted]), and then challenged in the validation or revalidation. For Observation 1(G)(ii), this will entail [redacted] In addition, as part of IC-014, during execution of the revalidation, all PPS used for each operational qualification ("OQ") and performance qualification ("PQ") will be documented so as to provide objective evidence. And, as part of IC-014, all PPS shall be listed in the Process Failure Mode Effects Analysis ("PFMEA") for risk analysis to patients.

3. To address the statistical rationale issue identified in Observation 1(G)(iii), Zimmer Biomet implemented *CP0972 Process Validation Sampling Plan* (see attachment 1E-J, *CP0972, Revision 1, Process Validation Sampling Plan*). The sampling plan in CP0972 uses a [redacted] approach to make appropriate confidence and reliability statements for acceptance.

4. To address the product requirements issue identified in Observation 1(G)(iv), Zimmer Biomet implemented QP 0114 (see attachment 1F-G, *QP 0114, Revision 1,* [redacted]), which defines product cleanliness requirements via [redacted]. Zimmer Biomet does not intend to validate a [redacted] method to determine final cleanliness of implants. For Observation 1(G)(iv), Zimmer Biomet will revalidate the [redacted] cleaning process for UHMWPE devices in compliance with appropriate product requirements and test method validations.

Pursuant to CAPA CA-02863, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 1(G)(i)-(iv);
2. Develop an implementation plan for CAPA CA-02863;
3. Develop a verification of effectiveness ("VoE") for CAPA CA-02863; and

Pursuant to parent CAPA CA-03092 (Cleaning Process Validations), Zimmer Biomet will conduct a system-wide investigation of its procedures for cleaning process validations that includes the following tasks:

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1. Conduct a root-cause analysis of the system-wide cleaning validation issues identified in Observations 1(E) through 1(H);
2. Harmonize validation requirement to implement elements of IC-014;
3. Update the Validation Master Plan;
4. Implement interim controls (b) (4) ;
5. Complete (b) (4) (b) (4) ;
6. Implement the harmonized cleaning requirements between the (b) (4) (b) (4) and the (b) (4) (b) (4) as set forth in (b) (4) ;
7. Evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75;
8. Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of all cleaning process validations;
9. Revalidate all cleaning processes at the Warsaw North Campus;
10. Complete CAPA CA-03092 (Cleaning Process Validations) implementation phase;
11. Verify effectiveness of CAPA CA-03092 (Cleaning Process Validations) and close CAPA.

With respect to the at least (b) (4) devices that were cleaned via the (b) (4) cleaning process for UHMWPE devices and then distributed between July 1, 2014, and October 13, 2016, Zimmer Biomet initiated a health hazard evaluation determination ("HHED") on October 27, 2016 (see attachment 1G-F, *HHED 10-2016-035*). The resulting health hazard evaluation ("HHE") was completed on December 16, 2016 (see attachment 1G-G, *HHE 2016-236*) (b) (4)

Completed Actions:

No.	Action	Completion Date
1G-1	Implemented *CP0972 Process Validation Sampling Plan* (see attachment 1E-J).	January 9, 2013
1G-2	(b) (4) (b) (4) (b) (4)	October 11, 2016
1G-3	(b) (4)	October 12, 2016
1G-4	(b) (4) (b) (4) (b) (4) (see attachment IG-E).	October 19, 2016

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No.	Action	Completion Date
1G-5	Implemented Interim Control IC 002, *Ultra High Molecular Weight Polyethylene (UHMWPE) Final Cleaning*, which details critical process parameters and requires documentation of these steps in the DHR (see attachment 1G-C).	October 20, 2016
1G-6	Implemented Interim Control IC-004, *Process Monitoring for Final Cleaning* (see attachment 1D-C)	October 20, 2016
1G-7	(b) (4) (b) (4)(b) (4) .	October 20, 2016
1G-8	Initiated CAPA CA-02863 to address the specific issues identified in Observation 1(G) regarding validation of the (b) (4) cleaning process for UHMWPE devices at the Warsaw North Campus (specifically Validation #PR53) (see attachment 1G-A).	October 26, 2016
1G-9	Initiated HHED 10-2016-035 (see attachment 1G-F).	October 27, 2016
1G-10	Implemented IC-014, (b) (4) , which employs an approach to validation practices in which all critical PPS are identified, subjected to (b) (4) and then challenged in the validation or revalidation (see attachment 1G-K).	November 1, 2016
1G-11	Implemented rationale to harmonize the (b) (4) cleaning processes at the (b) (4) (b) (4) with the (b) (4) cleaning processes at the (b) (4) (b) (4)	November 8, 2016
1G-12	Implemented Interim Control IC-030, (b) (4) to detail (b) (4) (see attachment 1G-D).	November 30, 2016
1G-13	Implemented Interim Control IC-031, (b) (4) (see attachment 1G-E).	November 30, 2016
1G-14	Initiated CAPA CA-03092 (Cleaning Process Validations) to address system-wide issues related to cleaning validations (see attachment 1E-A).	December 1, 2016
1G-15	Implemented QP (b) (4) to define product cleanliness requirements via testable residual limits (see attachment 1F-G)	December 16, 2016

Planned Actions:

No.	Action	Completion Date
1G-16	Complete efforts to harmonize the (b) (4) cleaning processes at the (b) (4) (b) (4) with the (b) (4) cleaning processes at the (b) (4) (b) (4) as set forth in (b) (4) .	(b) (4)
1G-17	Update Validation Master Plan.	(b) (4)

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1G-18	(b) (4) .	
1G-19	Complete testing on halted and low-risk products to provide assessment of containment so as to resolve products on hold.	
1G-20	Complete CAPA CA-03092 (Cleaning Process Validations) Root Cause / Action Plan phase.	
1G-21	Per CAPA CA-03092, evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75.	Target completion date to be reported in a future update
1G-22	Per CAPA CA-03092, revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of all cleaning process validations.	Target completion date to be reported in a future update
1G-23	Per CAPA CA-03092, revalidate all cleaning processes at the Warsaw North Campus.	Target completion date to be reported in a future update
1G-24	Complete CAPA CA-03092 (Cleaning Process Validations) implementation phase.	Target completion date to be reported in a future update
1G-25	Verify effectiveness of CAPA CA-03092 (Cleaning Process Validations) and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #1(H)

I. **Your firm's [redacted] cleaning process governed by work instruction *WIS0086* (Rev. 3, effective 10/13/2015) for sports medicine and microfixation devices manufactured out of [redacted] and [redacted] materials has not been adequately validated.**

The purpose of the most recent validation of this process (Validation #184, approved 8/5/2013) was to demonstrate the ability to remove [redacted] used during compression and injection molding. The following deficiencies were identified when reviewing Validation #184:

a. **The worst-case temperature conditions were not challenged during the validation and the actual settings used were not documented. The validation states that the process was run at nominal settings per *Process Engineering Specification 8.55. Process Engineering Specification 8.55* (Revs. 13, 14, and 15; effective since 10/16/2012 to the time of this inspection) defines an allowable [redacted] bath temperature range of [redacted] C.**

b. **The actual cleaning cycle times used during the validation were not documented. *Process Engineering Specification 8.55* (Revs. 13, 14, and 15; effective since 10/16/2012 to the time of this inspection) specifies a minimum cycle time of [redacted] minutes per cycle [redacted] cycles). As such, your firm could not provide objective evidence that a worst-case condition of [redacted] minutes per cycle was challenged.**

c. **When witnessing the process on 9/14/2016, we observed that the [redacted] cleaner was set to a power [redacted]) setting of [redacted] which could be manipulated by the operator. A required power setting was not established or challenged during the validation.**

d. **According to the validation protocol, devices were to be cleaned per *Process Engineering Specification 8. 55. Process Engineering Specification 8. 55* (Revs. 13, 14, and 15; effective since 10/16/2012 to the time of this inspection) instructs the operator to [redacted] during the cleaning process. The actual devices masses and [redacted] volumes used during the validation were not documented. As such, your firm could not provide**

objective evidence that worst-case solvent volume of [redacted] was challenged.

Between 7/1/2014 and 10/13/2016, your firm distributed at least [redacted] devices that were cleaned via this process.

Observation 1(H) Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03092 (Cleaning Process Validations) to address system-wide issues related to cleaning validations (see attachment 1E-A, *CAPA CA-03092 Summary*). During the recent inspection, FDA identified gaps in legacy Biomet cleaning validations at the Warsaw North Campus. As gaps in the cleaning validations were identified, Zimmer Biomet initiated CAPAs to address them, including:

CAPA	Date Initiated	Cleaning Description	Observation
CAPA CA-02953	October 12, 2016	(b) (4) cleaning process for knee femoral implants	Observation 1(E)
CAPA CA-02936	October 6, 2016	(b) (4) cleaning process for cleaning metal hip, extremities, knee, and trauma devices	Observation 1(F)
CAPA CA-02863	September 19, 2016	(b) (4) cleaning process for devices made of ultra high molecular weight polyethylene ("UHMWPE")	Observation 1(G)
CAPA CA-02855	September 15, 2016	(b) (4) cleaning process for sports medicine and microfixation devices manufactured from (b) (4) materials	Observation 1(H)

CAPA CA-03092, which is the parent CAPA for each of the above-listed cleaning-related CAPAs, presently is in the Investigation (Root Cause/Action Plan) Phase. Per CAPA CA-03092, Zimmer Biomet will evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75. Specifically, Zimmer Biomet will ensure that procedures, forms, and work instructions address:

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- Validating processes with a high degree of assurance;
- Validating processes according to established procedures;
- Documenting validation activities and results, including the individual approving the validation and the equipment validated;
- Monitoring and control of process parameters for validated processes; and
- Review and evaluation of changes or process deviations and resulting revalidation where appropriate.

Upon completion of the evaluation and revision of all cleaning process validation-related procedures, forms, and work instructions, Zimmer Biomet will revalidate all cleaning processes at the Warsaw North Campus. Documentation will be reviewed against revised procedures, forms, and work instructions and be remediated so as to conform to those revised procedures, forms, and work instructions.). Furthermore, in assessing cleanliness at the Warsaw North Campus, the standard from the , is the standard that is being used

* * *

To address the specific issues identified in Observation 1(H) regarding validation of the cleaning process for sports medicine and microfixation devices manufactured out of materials at the Warsaw North Campus (specifically Validation #PR184), Zimmer Biomet initiated CAPA CA-02855 on September 15, 2016 (see attachment 1H-A, *CAPA CA-02855 Summary*). CAPA CA-02855 presently is in the Investigation (Root Cause/Action Plan) Phase. Although the CAPA investigation is not complete, it appears that the root causes of the inadequacy of the validation of the cleaning process for sports medicine and microfixation devices manufactured out of materials (i.e., Validation #PR184) include inadequate procedures for validation activities and failure to follow procedures.

To contain the sports medicine and microfixation devices manufactured materials impacted by the cleaning validation issues identified during the inspection, (b) (4)

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		M459980				
		M639400				

(b) (4)
);

Specific corrections related to the observations in Observation 1(H)(i)-(iv) include implementing IC 014 (see attachment 1E-I, *IC 014, Revision 1,*), which employs an approach to validation practices in which all critical PPS are identified, subjected to and then challenged in the validation or revalidation.

1. For Observation 1(H)(i), this will entail , For example, the operational and performance qualification protocol test scripts (see attachment 1E-J, *ICF 014.10, Revision 1, OQ/PQ Protocol*) require documentation of all PPS used throughout the execution of the validation.

2. For Observation 1(H)(ii), this will entail [redacted] (see attachment 1E-N). [redacted] IC 014 (see attachment 1E-I). For example, the operational and performance qualification protocol test scripts (see attachment 1E-J) require documentation of all [redacted].

3. For Observation 1(H)(iii), this will entail establishing as a PPS [redacted] cleaning process for sports medicine and microfixation devices made with [redacted] (see attachment 1E-N). It will also entail documenting the [redacted] as required by IC 014 (see attachment 1-B). For example, the operational and performance qualification protocol test scripts for the [redacted] Cleaning System (see attachment 1E-J) require documentation of all PPS used [redacted]. Lastly, the equipment will be adequately qualified per IC 014, and more specifically [redacted] (b) (4) [redacted]

4. For Observation 1(H)(iv), this will entail [redacted] (see attachment 1E-N).

In addition, during execution of the revalidation, all PPSs used for each operational qualification ("OQ") and performance qualification ("PQ") will be documented so as to provide objective evidence as required by IC 014 (see attachment 1E-I). [redacted] Lastly, per IC 014, section 6.7.2 (see attachment 1E-I), all PPSs shall be listed in the Process Failure Mode Effects Analysis ("PFMEA") for risk analysis to patients.

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Pursuant to CAPA CA-02855, Zimmer Biomet will conduct an investigation that includes the following tasks:

- Conduct a root-cause analysis of the issues identified in Observation 1(H)(i)-(iv);
- Develop an implementation plan for CAPA CA-02855; and
- Develop a verification of effectiveness ("VoE") for CAPA CA-02855

Pursuant to parent CAPA CA-03092 (Cleaning Process Validations), Zimmer Biomet will conduct a system-wide investigation of its procedures for cleaning process validations that includes the following tasks:

- Conduct a root-cause analysis of the system-wide cleaning validation issues identified in Observations 1(E) through 1(H);
- Harmonize validation requirement to implement elements of IC 014;
- Update the Validation Master Plan (Cleaning Process Validations);
- [redacted]
- Complete [redacted] testing on halted and low-risk products to provide an assessment of containment and resolve product holds;
- Implement the harmonized cleaning requirements as between the [redacted] and the [redacted] as set forth in [redacted];
- Evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75;
- Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of all cleaning process validations;
- Revalidate all cleaning processes at the Warsaw North Campus;
- Complete CAPA CA-03092 (Cleaning Process Validations) implementation phase;
- Verify effectiveness of CAPA CA-03092 (Cleaning Process Validations) and close CAPA.

With respect to the at least [redacted] devices that were cleaned via the [redacted] cleaning process for sports medicine and microfixation devices made with [redacted] and [redacted] and then distributed between July 1, 2014, and October 13, 2016, Zimmer Biomet initiated a health hazard evaluation determination ("HHED") on September 30, 2016 (see attachment 1H-H, *HHED 09-2016-096*). The resulting health hazard evaluation ("HHE") was completed on

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December 15, 2016 (see attachment 1H-I, *HHE 2016-211*) (b) (4) .

Completed Actions:

No.	Action	Completion Date
1H-1	Initiated CAPA CA-02855 to address the specific issues identified in Observation 1(H) regarding validation of the (b) (4) cleaning process for sports medicine and microfixation devices made with (b) (4) at the Warsaw North Campus (specifically Validation #PR184) (see attachment 1H-A).	September 15, 2016
1H-2	(b) (4)	September 21, 2016
1H-3	Implemented Quality Hold 16-055-01 (see attachment 1H-B).	September 22, 2016
1H-4	Implemented Quality Hold 16-059-01 (see attachment 1H-C).	September 27, 2016
1H-5	Initiated HHED 09-2016-096 (see attachment 1H-H).	September 30, 2016
1H-6	Subjected sports medicine and microfixation devices made with (b) (4) (b) (4)	October 7, 2016
1H-7	Implemented Quality Hold 16-068-01 (see attachment 1B-G).	October 12, 2016
1H-8	Implemented IC 014, which employs an approach to validation practices in which all critical PPS are identified, subjected to (b) (4) and then challenged in the validation or revalidation (see attachment 1-B).	November 1, 2016
1H-9	Initiated an effort to harmonize the (b) (4) cleaning processes at the (b) (4) (b) (4) with the (b) (4) cleaning processes at the (b) (4) (b) (4)	November 8, 2016
1H-10	Initiated CAPA CA-03092 (Cleaning Process Validations) to address system-wide issues related to cleaning validations (see attachment 1E-A).	December 1, 2016
1H-11	Initiated HHE 2016-211 (see attachment 1H-I).	December 15, 2016

Planned Actions:

No.	Action	Completion Date
1H-12	Complete efforts to harmonize the (b) (4) cleaning processes at the (b) (4) (b) (4) with the (b) (4) cleaning processes at the (b) (4) (b) (4) as set forth in (b) (4)	(b) (4)
1H-13	Update Validation Master Plan.	(b) (4)

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No.	Action	Completion Date
1H-14	(b) (4)	(b) (4)
1H-15	Complete (b) (4) testing on halted and low-risk products to provide assessment of containment so as to resolve products on hold.	(b) (4)
1H-16	Complete CAPA CA-03092 (Cleaning Process Validations) Root Cause / Action Plan phase.	(b) (4)
1H-17	Per CAPA CA-03092, evaluate all procedures, forms, and work instructions associated with process validation for cleaning processes at the Warsaw North Campus to ensure that such process validations are compliant with the requirements of 21 C.F.R. § 820.75.	Target completion date to be reported in a future update
1H-18	Per CAPA CA-03092, revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of all cleaning process validations.	Target completion date to be reported in a future update
1H-19	Per CAPA CA-03092, revalidate all cleaning processes at the Warsaw North Campus.	Target completion date to be reported in a future update
1H-20	Complete CAPA CA-03092 (Cleaning Process Validations) implementation phase.	Target completion date to be reported in a future update
1H-21	Verify effectiveness of CAPA CA-03092 (Cleaning Process Validations) and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #1(I)

J. Your firm's molding process used to manufacture bar stock out of) failed to meet acceptance criteria during validation. our firm manufactures bar stock of several different diameters, with the version being the largest. The bar stock is manufactured out of ", which presented the greatest challenge during Validation #42, Addendum #1 (approved 2/22/2010) because During the validation, used to manufacture bar stock out of failed to meet mechanical testing acceptance criteria. Despite this, your firm continues to manufacture bar stock as of 9/9/2016. *QPOOO1* (Revs. 6 through 10; effective 3/17/2010 to 10/20/2016) requires that for "non-validated" item numbers such as *(i.e.,* that which failed to meet acceptance criteria during validation), each manufactured lot is tested for tensile strength, density, and percent crystallinity. Your firm's Manufacturing Manager explained that has historically been tested from each lot. This practice is inadequate to assure the bar stock meets all quality requirements because the molding process is not fully verifiable.

Between 3/1/2010 and 9/19/2016, your firm distributed at least devices manufactured out of bar stock. Also, between 3/1/2010 and 11/1/2016, your firm distributed inches of bar stock to other Zimmer Biomet facilities for their manufacturing of finished devices.

Observation 1(I) Investigation and Response:

During the recent inspection, on September 19, 2016, Zimmer Biomet initiated CAPA CA-02862 to address the issues identified in Observation 1(I) (see attachment 1I-A, *CAPA CA-02862 Summary*). CAPA CA-02862 is currently in the implementation phase. In addition, on December 12, 2016, Zimmer Biomet initiated CAPA CA-03121 (Systemic Improvements to Process Validation System) to address system-wide issues concerning process validation activities at Zimmer Biomet's Warsaw North Campus (see attachment 1-A, *CAPA CA-03121*

(b) (4) CAPA CA-03121 currently is in the Investigation (Root Cause/Action Plan) Phase.

As noted in Observation 1(I), Zimmer Biomet uses an (b) (4) process to manufacture ultra high molecular weight polyethylene (b) (4) bar stock from (b) (4) . The (b) (4) molding process consists of (b) (4) bar stock is manufactured (b) (4) . Prior to the inspection, Zimmer Biomet was manufacturing (b) (4) bar stock made from (b) (4)) via a process not validated (b) (4) . The (b) (4) bar stock made from (b) (4) (b) (4) was not validated because the (b) (4) " used to manufacture such bar stock failed to meet mechanical testing acceptance criteria in Validation #42, Addendum #1, (b) (4) (Validation #42 was approved (b) (4)). Upon completion of Validation #42, Zimmer Biomet implemented lot testing/release of the (b) (4) bar which consisted of (b) (4) being (b) (4) . This process remained in place until the process was halted on September 20, 2016, during the inspection. The CAPA (b) (4) (b) (4) (b) (4) , (b) (4)

Zimmer Biomet has taken steps to contain product affected by the issues identified in Observation 1(I). (b) (4) Zimmer Biomet determined that no (b) (4) bar stock made from (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) s(b) (4) (b) (4)

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1. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) ;
2. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) ;
3. (b) (4) (b) (4) ;
4. (b) (4) inspection is completed at the (b) (4) ; and
5. (b) (4) (b) (4)) (b) (4) .

Finally, on November 3, 2016, Zimmer Biomet discontinued production (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)) (b) (4)

Pursuant to CAPA CA-02862, Zimmer Biomet conducted an investigation that included the following tasks:

1. Review the validation for manufacturing (b) (4) bar stock (Validation #42) to ensure that all (b) (4) bar stock item numbers are covered by the validation;
2. Initiate an HHED for distributed products manufactured using (b) (4) bar stock made from (b) (4) ;
3. Conduct a root-cause analysis of the issues identified in Observation 1(l);
4. Perform quality records search to identify previous occurrences, if any, of the issues identified in Observation 1(l);
5. Develop an implementation plan for CAPA CA-02862; and
6. Develop a verification of effectiveness ("VoE") plan for CAPA CA-02862.

Going forward under CAPA CA-02862, Zimmer Biomet will review and update the process failure mode, effects, and criticality analysis ("PFMECA") for (b) (4) to ensure that appropriate risks are included for all associated critical features, including (b) (4) (b) (4) (b) (4) (b) (4) under CAPA CA-03121 ((b) (4)).

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Completed Actions:

No.	Action	Completion Date
1I-1	Initiated CAPA CA-02862 to address the issues identified in Observation 1(I) (see attachment 1I-A).	September 19, 2016
1I-2	(b) (4) b) (4) (b) (4) (b) (4) (b) (4) (b) (4) .	September 20, 2016
1I-3	(b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	September 20, 2016
1I-4	Completed HHED 09-2016-093 (see attachment 1I-E).	September 29, 2016
1I-5	Initiated HHE 2016-212 (see attachment 1I-F, *HHE 2016-212*).	October 20, 2016
1I-6	Determined root cause (see attachment 1I-C).	October 31, 2016
1I-7	Performed a quality records search to identify previous occurrences, if any, of the issues identified in Observation 1(I).	October 28, 2016
1I-8	(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)	November 3, 2016
1I-9	Complete Root Cause / Action Plan Phase	November 18, 2016
1I-10	Developed an implementation plan for CAPA CA-02862.	December 12, 2016
1I-11	Developed a VoE plan for CAPA CA-02862.	December 12, 2016
1I-12	Initiated CAPA CA-03121(see attachment 1-IB).	December 12, 2016

Planned Actions:

No.	Action	Completion Date
1I-13	Review and update the PFMECA for (b) (4) to ensure that appropriate risks are included for consolidation and validation	(b) (4)
1I-14	Create separate work centers for (b) (4) CIPs	(b) (4)
1I-15	Modify routings to specify proper CIP work center	(b) (4)
1I-16	Update Procedure WI0012	(b) (4)
1I-17	Complete CAPA CA-02862 Implementation Phase.	(b) (4)
1I-18	Verify effectiveness of CAPA CA-02862 and close CAPA.	(b) (4)

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FDA Observation 2

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FDA Observation #2A

Procedures to control environmental conditions have not been adequately established.

Specifically,

A. Your procedures for monitoring the quality of in-process water used throughout your facility are inadequate in that:

i. Since 2005, the (b) (4) Water System has processed water for use in manufacturing, cleaning, and passivating medical devices, but your firm has not adequately monitored this system's water quality in accordance with established procedures. QP0049 (b) (4) Water (b) (4) Monitoring was first issued 11/14/2007 to monitor total heterotrophic count, endotoxin, conductivity, and total organic carbon at a frequency of (b) (4). Your firm has no objective evidence that conductivity and total organic carbon monitoring has occurred since the system was installed. Your firm's management explained that the "Scope" section of this procedure states that it provides the monitoring "methods and frequencies for validated water systems." As of 09/09/2016, your firm's management confirmed that a validation has never been completed for the (b) (4) Water System and that OQ/PQ validation activities under Validation Protocol 204 Rev. 2 are still in progress. From 09/24/2014 to 11/19/2016, your firm has been collecting water system testing results so they can be compared to the alert and action limits that will be established upon completion of Protocol 204 Rev. 2. However, you firm has no documented evaluations of these testing results to determine if this system is in control and suitable for its intended use. Comparison of this testing data to your firm's preliminary alert and action limits identified in Protocol 204 Rev. 2 revealed the following:

Test Type	Action Limit Failures	Alert Limit Failures	Total Failures
Conductivity	11	1	12
Endotoxin	2	2	4
Microbial	3	0	3
Total Organic Carbon	0	2	2
Totals	16	5	21

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Water from this system is utilized in the following:

a. **Direct product contact during**

1. **(b) (4) - Water supplied to the rinse tanks in the (b) (4) line (b) (4)) and the (b) (4))**
2. **Final Cleaning- Knee Miraclean (b) (4) and manual cleaning of Poly (b) (4)), trauma Metals (b) (4) , and Sports Medicine devices (b) (4)) using (b) (4))**
3. **Potentially impacted products include 11,221 unique part numbers. (b) (4)**

b. **Indirect product contact during:**
   1. **Preparation of (b) (4) that is used for sanitization of all Environmentally Controlled Areas within (b) (4)**
   2. **Potentially impacts all sterile products packaged in (b) (4) .**

ii. **Evaluations are not consistently performed when action limits are exceeded or when a point of use consistently fails to meets specification. From 07/01/2014 to 09/01/2016, your firm has documented thirteen (13) water samples in which alert and/or action limits were exceeded in (b) (4) Seven (7) of these water samples exceeded microbial alert/action limits, five (5) samples exceeded endotoxin alert limits, and one (I) water sample exceeded Total Organic Carbon alert limits. Of these excursions:**

a. **Three (3) out of the thirteen (13) failed water samples involved exceeding the alert limit in the (b) (4) Cleanroom Gowning Room (b) (4) in samples collected from the (b) (4) handwashing sinks.**

Procedure	Date	Test Failed	Alert/Action Limits	Sample Result	Retest Value
QP0021	7/21/14	Microbial - (b) (4)	(b) (4)	64	1
QP0024	7/21/14	Endotoxin - (b) (4)	(b) (4)	0.314	0.0125
QP0024	7/21/14	Endotoxin - (b) (4)	(b) (4)	0.369	0.0726

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There was no documented evaluation of these samples to determine if there was any product impact. Notably, during routine environmental monitoring, your firm documented two (2) microbial contact plate samples that exceeded action limits in the (b) (4) Cleanroom on 07/22/2014. The corresponding QP0014 Alert/ Action Level Corrective Action Report for these contact plate failures showed that samples were retested on 08/09/2014 with acceptable results and that all procedures were being followed. The report concluded "No adverse events anticipated "with a justification of" All processes and procedures were followed."

b. Two (2) out of the thirteen (13) failed water samples involved exceeding alert limits in the process water sampled from the (b) (4) rinse tank in the (b) (4) Work Environment (b) (4) For example:

Procedure	Date	Test Failed	Alert/Action Limits	Sample Result	Retest Value
QP0021	7/21/14	Microbial	(b) (4)	113	4
QP0024	10/10/14	Endotoxin	(b) (4)	0.429	0.131

Subsequent retests passed, but no corrective actions were taken. The (b) (4) tank is the first physical interaction with medical devices after the (b) (4) Of note, your firm's most recent revision of QP0049, version 6 effective 01/21/2015, increased the alert/action limits of microbial counts and endotoxins for process water in (b) (4) The microbial alert and action limits became (b) (4) CFU/ml and (b) (4) CFU/ml while the endotoxin alert and action limits became (b) (4) EU/ml and (b) (4) EU/ml. Your firm's Regulatory Compliance Manager in charge of revision control for this procedure stated the limits changed based upon reviews of historical data for the water system.

c. Eight (8) out of fourteen (14) failed samples involved retests that were found acceptable with no further actions taken. Five (5) of the eight (8) had no documented evaluations of the failures to determine if there was any product impact. Of these:
1. **One (1) sample involved microbial action limits being exceeded.**
2. **Four (4) samples involved alert limits for endotoxins being exceeded on 07/21/2014, 09/18/2014, 10/10/2014, and 12/09/2014. These samples were part of your firm's (b) (4) monitoring program under QP0024.**

d. Seven (7) out of fourteen (14) failed samples were missing QP0014 Alert/ Action Level Corrective Action Reports which are required documentation according to your firm's Corrective Action Guidelines- Microbial Monitoring procedure, QP0027 version 2

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effective 05/31/2013. As a result, your firm has no documentation showing that these failures were evaluated to determine if there was any impact to product.

Observation 2A Investigation and Response:

On November 30, 2016, Zimmer Biomet opened CAPA CA-03072 to investigate and address the findings in Observation 2(A) regarding the monitoring of the quality of in-process water from the and water systems for (see attachment 2A-A, *CAPA CA-03072 Summary*). CA-03072 is in the Investigation Phase.

As explained in the response to Observation 1(D), Zimmer Biomet is committed to re-validating the water systems at the Warsaw North Campus. The revalidation will be accompanied by a new sampling and monitoring plan appropriate to (i) confirm that the validated state of the water systems is maintained and (ii) fully evaluate any future excursions and out of limit results. Upon validation completion, all procedures affecting water system operation, monitoring, and maintenance will be updated to ensure water quality per the new validated requirements. Until such time that the revalidation can be completed and a new process for monitoring of the water systems can be implemented, Zimmer Biomet has taken and will continue to take several containment actions to ensure that product is not negatively impacted by gaps in the original water system validations and the process for monitoring the quality of the in-process water.

First, as explained in the cover letter to this response, during the inspection Zimmer Biomet implemented (b) (4) (b) (4) .

Second, , Zimmer Biomet completed a Health Hazard Evaluation ("HHE") on December 20, 2016 to assess the potential product safety impact of the gaps in monitoring of in-process water and lack of evaluation of excursions (as well as the gaps in the water system validations discussed in the response to Observation 1(D)) (see attachment 2A-C, *HHE #2016-307*). In addition, Zimmer Biomet is conducting a review of water monitoring data to determine the potential impact, if any, on previously produced product. The review will include an analysis of previously recorded excursions, including those identified in Observation 2(A) and Observations 1(D)(i)(c) and 1(D)(ii)(c).

Third, , all product produced at the Warsaw North Campus will be evaluated per IC 004. IC 004 describes the necessary process monitoring requirements to ensure product cleanliness is maintained to pre-determined Zimmer Biomet requirements for endotoxin, debris, cytotoxicity, and TOC (see attachment 2A-D, *IC 004, Process Monitoring of Final*

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Cleaning). On December 14, 2016, Zimmer Biomet trained appropriate personnel to the requirements of the Interim Control IC 004 (see attachment 2A-E, *IC 004 Training Records*).

Further, to allow continued manufacturing and cleaning operations at the Warsaw North Campus, Zimmer Biomet implemented Interim Control IC 036 on December 15, 2016 to govern monitoring activities for the water system (see attachment 2A-F, *IC* 036). On December 19, 2016, Zimmer Biomet trained appropriate personnel to the requirements of the Interim Control, including associated forms (see attachment 2A-G, *IC 036 Training Records*). IC 036 provides for increased monitoring of the water systems and contains processes for sampling, excursion investigations, and excursion escalation. Under the increased monitoring requirements, Zimmer Biomet will sample and test both water systems for total organic carbon ("TOC"), endotoxins, conductivity, and heterotrophic plate count. The systems will then be sanitized and then the systems will be sampled again to identify post sanitization conditions. . Increasing the monitoring frequency will allow Zimmer Biomet to evaluate the system over time to determine if the system is in control. Under IC 036, improved reaction to excursions will ensure proper response and escalation to exceeding results. Additionally, greater attention to change control requires prior approval of changes and ensures documentation of the system updates and evaluates the impact to the system.

Until Zimmer Biomet completes the full revalidation of the water systems at the Warsaw North Campus and implements a related monitoring plan, Zimmer Biomet will continue to monitor the water at the Warsaw North Campus under IC 036. The use of IC 036 will ensure that the gaps in the previous process for monitoring water will not recur. Specifically, with respect to Observation 2(A)(i), IC 036, section 6 requires that the initial sampling frequency and any subsequent change to the sampling frequency, sanitization frequency, or any other change to the system will be documented on ICF 036.3 as part of change control. The initial increased monitoring will require Zimmer Biomet to sample and test the appropriate ports for TOC, endotoxins, conductivity and heterotrophic plate count. Zimmer Biomet will provide evidence in a future update to demonstrate that this monitoring is occurring under IC 036.

Further, section 7.7 of IC 036 also governs the evaluation and escalation of any excursions identified during monitoring of in-process water. Specifically, the Interim Control requires that when results exceed action limits, the occurrence shall be investigated immediately. Exceeded action limits will first be investigated to determine if the test is valid by . If it is determined that the test is invalid, then an immediate resample of the location will be required; however, a non-conformance investigation will not be required. If it is determined that the test is valid, then the excursion will be evaluated by an Issue Evaluation ("IE") per the CAPA Process under QM 14.0, *Corrective and Preventative Action*. With respect to the out of limit results identified in both Observations 2(A)(i) and 2(A)(ii), Zimmer Biomet will conduct a evaluation of the action and alert limit failures identified by FDA in the Observations. Zimmer Biomet will complete an

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HHE to determine what, if any, risks are posed by the documented excursions and gaps in the previous validation activities for the (b) (4) water system and the potential impact on the safety of product in the field.

In addition, Zimmer Biomet will revise procedures QP 0021, (b) (4) ; and QP 0049, (b) (4) , to provide direction regarding the proper technique for obtaining samples from the water system as directed in IC 036. Our preliminary review of the method for collecting water samples indicates that operators may be inadvertently introducing contaminants into the monitoring samples. Following the implementation of IC 036, Zimmer Biomet will re-train personnel on proper water sampling techniques.

Finally, as described in HHE 2016-307, Zimmer Biomet is confident that the (b) (4) testing implemented under Interim Control IC 004 ensures that product manufactured, processed, and cleaned at Warsaw North Campus under the current water system meets Zimmer Biomet's requirements for endotoxin, TOC, cytotoxicity, and debris despite the identified gaps in the previously conducted system validation. No product is released for distribution if it fails (b) (4) , providing assurance that the water system is operating under a state of control sufficient to permit continued operations while the new validation is pending.

Completed Actions:

No.	Action	Completion Date
2A-1	(b) (4)	September 29, 2016
2A-2	Initiated CAPA CA-03072 to address the issues identified in Observation 1(D) (see attachment 2A-A).	November 30, 2016
2A-3	Confirmed that the total organic carbon ("TOC") containers are certified low TOC (less than (b) (4) ppb) to verify that TOC excursions were not due to carbon leaching from the sampling bottles (see attachment 2A-I).	December 8, 2016
2A-4	Initiated HHED #12-2016-033 to assess the potential product safety impact of the gaps in the water system validations identified in Observation 1(D) (see attachment 2A-H).	December 14, 2016
2A-5	Implemented Interim Control IC 036 for increased monitoring of water systems and to govern sampling, excursion investigations, and excursion escalation (see attachment 2A-F)	December 15, 2016
2A-6	Implemented IC 004, *Process Monitoring of Final Cleaning*, to describe the necessary process monitoring requirements to ensure product cleanliness is maintained to pre-determined Zimmer Biomet requirements for endotoxin, debris, cytotoxicity, and TOC (see attachment 2A-D).	October 21, 2016

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2A-7	Trained appropriate personnel to the requirements of the IC 036 (see attachment 2A-G).	December 19, 2016
2A-8	Trained appropriate personnel to the requirements of the IC 004 (see attachment 2A-E).	December 14, 2016

Planned Actions:

No.	Action	Completion Date
2A-9	Identify and label sample sites to meet GMP requirements and clarify sampling plan.	(b) (4)
2A-10	Retrain personnel on proper water sampling techniques after implementation of IC 036.	(b) (4)
2A-11	(b) (4) .	(b) (4)
2A-12	Review (b) (4) and determined (b) (4)	(b) (4)
2A-13	Revise procedures QP 0021, QP 0024, and QP 0049 to provide detailed directions regarding sampling techniques as directed in IC 036.	(b) (4)
2A-14	Completion of the Root Cause/Action Plan Phase	(b) (4)
2A-15	Complete CA-03072 Implementation Phase.	Target completion date to be reported in a future update
2A-16	Verify effectiveness of CA-03072 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #2B

B. Your firm's Zimmer Biomet Environmentally Controlled Room Specifications Standard Operating Procedure, SOP 9.5. 9 Rev. 13 effective 05/10/2016, identifies rooms containing processes "of such a nature that controls are necessary to prevent adverse effects on product" as well as the level of controls to be imposed on those rooms. This procedure is inadequate in that:

i. There is inadequate assurance that the particle counts measured in the cleanrooms accurately represent particulate concentrations in those environments. For example:

a. Your firm's Monitoring Air-Controlled Environments procedure, QP0013 Ver. 7 dated 01/21/2015, states in section 5.2 "Each particle count will consist of a volume of air equal to [redacted]." From 07/01/2014 to 10/12/2016, your firm's sample size was 1 cubic foot (0.0283 cubic meters) which is [redacted] times less than required by this procedure.

b. Locations for particle counting are not adequately defined and, therefore, air sampling is not performed in a manner that is consistently representative of routine room conditions. During a tour of the [redacted] cleanroom gowning area, interviews with an environmental monitoring operator revealed that the particle counter can be placed in one of two different locations that are approximately [redacted] feet away from each other on opposite sides of the room. These locations are as follows:

1. [redacted]

2. [redacted]

ii. Your firm claims conformance to ISO 14644-1:2015 in SOP 9.5.9, however, particle monitoring methods used in cleanrooms are not conducted in accordance with the standard in that:

a. Your firm's determination of the quantity of sampling locations within a given cleanroom does not meet the minimum requirements identified in section A.4.1 of the standard. This section requires the minimum number of locations to be based on the area of the cleanroom represented in square meters. For example:

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1. **The [redacted] Packaging Cleanroom, [redacted] represents a total area of [redacted] square feet [redacted] square meters). Per the standard, the minimum number of sample locations must be [redacted]. In this cleanroom, your firm has identified and routinely monitors nine (9) sampling locations, which represents approximately [redacted]% of the required number. There is no documented rationale for using this number of sampling locations.**

2. **The [redacted] Cleanroom, [redacted] is used to package all [redacted] metals products [redacted] and represents a total area of [redacted] square feet ([redacted] square meters). Per the standard, the minimum number of sample locations must be 23. In this cleanroom, your firm has identified and routinely monitors (9) sampling locations, which represents approximately [redacted] of the required number. There is no documented rationale for using this number of sampling locations.**

b. **Your firm's positioning of sampling locations does not demonstrate compliance with section A.4.2 of the standard. This section specifies that the minimum number of samples [redacted]. Maps of routine sampling locations are not drawn to scale and do not provided objective evidence that [redacted] There is no documented rationale for selecting these positions for the sampling locations.**

c. **Your firm's sampling time does not meet the minimum specified in section A.4 of the standard. This section requires a minimum sample time of [redacted]. Review of settings for your firm's particle counter (Asset [redacted], model [redacted]) revealed the sample time was 33 seconds. Your firm's environmental monitoring operators confirmed that all particle counters at your facility use the same sampling settings and that these settings would have been used for all samples taken in all cleanrooms from 07/01/2014 to 09/01/2016.**

iii. **Work environments (WEs) and controlled environments (CEs) are not adequately maintained to ensure product that has been cleaned and/or passivated will not become contaminated by particulates and microorganisms. During tours of your WEs and CEs, we observed the following:**

a. **On 09/13/2016, three (3) different desk fans(~8" diameter) were observed in operation at three different stations in the [redacted] WE. All three (3) fans were visibly soiled with apparent grayish dust/debris with one (1) blowing onto the operator approximately 12" above lot# [redacted]) that was just removed from an [redacted] cleaning bath.**

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b. During operations 09/28/2016, supply and/or return vents in your firm's Poly WE, Sports Med CE, Knees WE, and Metals WE were found to have apparent grayish dust/debris present on the vent surfaces. (b) (4) out of (b) (4) total vents exhibited these visual characteristics with one (1) out of (b) (4) being a grate that housed a HEPA filter in the Knees WE within approximately (b) (4) on which carriers containing passivated devices are offloaded.

iv. From 07/01/2014 to 09/01/2016, your firm documented 292 instances of exceeding alert and/or action limits. Excursions were broken down into the following types: 75 Continuous Particulate Monitoring (b) (4) 43 Microbial Surface, 26 Microbial Air, 14 Humidity, 65 Pressure, 20 Particulate, 34 Microbial Air and Surface, 10 No Pressure, 8 Air flow, 6 Microbial Surface and Personnel, and 1 Microbial Personnel. Further review of 1hese excursions revealed 1hat corrective actions are not consistently taken when action limits are exceeded For example:

a. 22 excursions had no documented Corrective Action form as required by your firm's Alert/ Action Level Corrective Action Report procedure, QP00014 rev. 8 effective 04/12/2013. Your firm has no documented assessments of these excursions to determine if there was any product impact. Examples of these excursions include:

Room #	Room Type	Date	Test	Excursion (Qty)	Examples of Products Processed Through Room on Excursion Date
(b) (4)	Cleanroom	8/21/14	Microbial Air and Surface	6	(b) (4)
(b) (4)	Cleanroom	11/19/14	Microbial Air and Surface	4	(b) (4)
(b) (4)	Cleanroom	8/21/14	Microbial Air	1	(b) (4)

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b. 54 action limit excursions resulted in no corrective actions being taken with 16 excursions occurring when there were no operators present during sampling. In place of corrective actions, retests of the locations were performed with the following results:

1. 31 excursions had acceptable retests with conclusions of "All procedures were being followed." For example:

Room #	Room Type	Date	Test	Excursion (Qty)	Examples of Products Processed Through Room on Excursion Date
(b) (4)	Cleanroom	07/14/16	Microbial Air and Surface	4	(b) (4)
(b) (4)	Cleanroom	02/08/16	Microbial Air and Surface	3	(b) (4)
(b) (4)	Work Env.	06/16/16	Microbial Air and Surface	4	(b) (4)

2. One (1) action limit excursion had a retest that also failed the action limits with the report concluding "All procedures were being followed" and no further actions were taken.

Room #	Room Type	Date	Test	Action Limit	Initial Test	Retest
(b) (4)	Work Env.	06/16/16	Microbial Air	(b) (4) CFU	(b) (4) CFU	(b) (4) CFU

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v. Rooms classified as the same general category (i.e. work environment, controlled environment, cleanroom) do not have the same levels of control/monitoring although SOP 9.5.9 considers them equivalent by definition. For example:

a. Work Environments (WE) do not exhibit the same levels of controls even though they contain similar operations with similar risks. For example:

1. For the [redacted] WE, there is a [redacted] line and subsequent inspection step. Product families passing through this WE [redacted]) include [redacted]. However:

i. The [redacted] line is open to the uncontrolled manufacturing environment on one side [redacted]. Air flow passes through a HEPA filter above the inspection table, but is supplied by the main HV AC system that recirculates and supplies air to the rest of the uncontrolled manufacturing area.

ii. Work Environment Room Rules. Gowning and Ungowning procedure, INST 9.5.8.12 rev. 1 effective 08/29/2016, [redacted] Personnel gown in the main uncontrolled manufacturing environment in proximity to machining operations.

iii. According to INST 9.5.9.23 Rev. 3, microbial surface and air monitoring is performed [redacted]. Your firm's alert/action limits for surface monitoring are [redacted] CFU and [redacted] CFU while the microbial air monitoring is [redacted] CFU and [redacted] CFU

2. For the [redacted] Product families passing through this WE include [redacted]. However:

i. The room is physically separated from uncontrolled environments by slatted plastic contains, but the dedicated HV AC system that supplies tl1e room with air flow utilizes [redacted] located in a hallway in an uncontrolled environment outside of the WE. The air vents that supply air to this room are not filtered by HEPAs.

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ii. INST 9.5.8.12 rev. 1 requires [redacted] Personnel gown in an uncontrolled environment in which packaged devices are boxed in preparation for shipment to the sterilizer.

iii. According to INST 9.5.9.21 Rev. 3, microbial surface and air monitoring is performed [redacted]. Your firm's alert/action limits for surface monitoring are [redacted] CFU and [redacted] CFU while the microbial air monitoring [redacted] CFU and [redacted] CFU

3. For the [redacted]), an [redacted] line off-loads carriers containing exposed devices to the WE. Product families passing through this WE include [redacted]. However:

i. The room is physically separated from uncontrolled manufacturing environments by hard walls and doors. The dedicated HV AC system provides partially recirculated air through supply vents and return vents that span the WE as well as the adjacent controlled environment and cleanroom. Supply vents for all [redacted] rooms are HEPA filtered.

ii. INST 9. 5. 8.12 rev. 1 requires [redacted]. Personnel gown in an ISO Class 8 Gowning Room adjacent to the WE.

iii. According to INST 9.5.9.25 Rev. 2, microbial surface and air monitoring is performed [redacted]. Your firm's alert/action limits for surface monitoring are [redacted] CFU and [redacted] CFU while the microbial air monitoring is [redacted] CFU and [redacted] CFU

b. Your firm identifies Resorbable Tech [redacted]), Sports Med [redacted]), and Bag Mfg. [redacted]) as controlled environments, but they do not share the similar levels of control. For example:

1. Per INST 9.5.9.19 rev. 3 effective 8 Jan 2015, the Biomet Sports Medicine Controlled Environment Room ([redacted]) requires Surface Monitoring (Contact Plates) and Air Sampling (Air Strips) to be monitored [redacted].
2. Per INST 9.5.9.17 rev 3 effective 30 Dec 2014, the Resorbable Tech Controlled Environment Room [redacted] requires Cleaning to be performed [redacted]

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3. **Per INST 9.5.9.15 rev. 11 effective 06/1112015, the Bag Manufacturing Controlled Environment [redacted] requires Differential Pressure, Temperature, and Relative Humidity to be monitored [redacted] Particulate Counts, Air Flow- Supply, and Air Flow- Return to be monitored [redacted]; and Surface Monitoring (Contact Plates) and Air Sampling (Air Strips) to be monitored [redacted]**

From 07/01/2014 to 09/09/2016, your firm has manufactured and distributed at least [redacted] devices that have been processed through cleanrooms in [redacted].

Observation 2B Investigation and Response:

On October 14, 2016, Zimmer Biomet opened CAPA CA-02965 (see attachment 2B-A, *CAPA CA-02965 Summary*) to investigate and address the findings in Observation 2(B)(i) and 2(B)(ii) regarding the environmental monitoring process for obtaining particulate counts and the related finding regarding the failure to fully adhere to ISO standard 14644-1:2015 (Cleanrooms and associated controlled environments -- Part 1: Classification of air cleanliness by particle concentration). CA-02965 is in the Investigation (Root Cause/Action Plan) Phase. In addition, on September 21, 2016, Zimmer Biomet opened CAPA CA-02872 (see attachment 2B-B, *CAPA CA-02872 Summary*) to investigate and address the findings in Observations 2(B)(iii), 2(B)(iv), and 2(B)(v) regarding the environmental control of work environments and controlled environments and the failure to investigate excursions and out of limit results for environmental monitoring in cleanrooms and work environments. CA-02872 is in the Investigation (Root Cause/Action Plan) Phase.

(b) (4) [redacted]. A work environment is distinguished from a manufacturing environment in that it is a physical enclosure of some form, [redacted]. On the other hand, controlled environments ("CEs") were those environments that do not require controls to meet specific standards, but where the process is of such a nature that controls are necessary to prevent adverse effects to product. These rooms are similar to cleanrooms except the amount of control, monitoring, and the extent of gowning is reduced. Finally, cleanrooms are an environment requiring controls to meet the requirements of industrial standards such as BS EN ISO 14644-1 and BS EN ISO 14644-2, BS EN ISO 13408-1, and/or USP requirements, as applicable. Going forward, Zimmer Biomet is simplifying these categorizations by using the term cleanroom or work environment only. The definition of the term "cleanroom" remains the same. IC 001, [redacted] see attachment 2B-C, *IC-001 Rev. 2*), defines [redacted]. The previously termed work environments and controlled environments have

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been evaluated for intended use and Zimmer Biomet determined that all may be appropriately be considered work environments.

CA-02965 / Observations 2(B)(i) and 2(B)(ii)

During the inspection on September 29, 2016, Zimmer Biomet [redacted] (b) (4) [redacted]. (b) (4) [redacted] ,(b) (4) [redacted].

Zimmer Biomet instituted Interim Control IC-001 during the inspection on October 28, 2016 and instituted Rev. 2 of IC-001 on November 9, 2016. IC-001 contains the environmental monitoring elements of ISO 14644-1 for particle counts, including the elements of the standard that are identified in Observations 2(B)(i) and 2(B)(ii). This Interim Control was initiated prior to re-starting production in the applicable areas. Specifically, IC-001 ensures that:

- the proper volume of air is sampled (i.e., [redacted]) in section 7.1.4, addressing Observation 2(B)(i)(a);
- the sample is obtained for the proper duration (i.e., [redacted]) in section 7.1.4, addressing Observations 2(B)(i)(a) and 2(B)(ii)(c); and
- the proper control of room diagrams and assessment of changes to the room and diagrams prior to implementing changes, addressing Observations 2(B)(i)(b) and 2(B)(ii)(b). Additionally, a clear definition of particulate counting locations is now provided in the recently revised drawing located in the following instructions ("INST") (see attachment 2B-D, *Cleanroom INSTs*):
    - INST 9.5.9.1, November 15, 2016; [redacted] Cleanroom/Gown Room Specification
    - INST 9.5.9.10, November 15, 2016; [redacted] Cleanroom/Gown Room Specification
    - INST 9.5.9.12, November 15, 2016; [redacted] Cleanroom/Gownroom Specification
    - INST 9.5.9.13, November 15, 2016; [redacted] Cleanroom/Gownroom, and [redacted] Package and Assembly Room Specification
    - INST 9.5.9.14, November 11, 2016; [redacted] Fill, Clean Rooms, Gowning Rooms Specification
    - INST 9.5.9.15, November 15, 2016; [redacted] Clean rooms/Gown rooms/Work Environments Room Specification
    - INST 9.5.9.19, November 15, 2016; [redacted] Room Specification
    - INST 9.5.9.21, November 15, 2016; [redacted] Environment Room Specification
    - INST 9.5.9.22, November 15, 2016; [redacted] Environment Room Specification
    - INST 9.5.9.24, November 15, 2016; [redacted] Cleanroom/Gown Room Specification

- INST 9.5.9.25, November 15, 2016; [redacted] Environment Room Specification

In addition, IC-001 section 7.2 contains processes for investigation of cleanroom excursions and an escalation process for the consideration and evaluation of excursions. This element of the interim control addresses the finding in Observation 2(B)(iv) regarding cleanrooms (as well as WEs, which are discussed in more detail below). Further, to address Observation 2(B)(ii)(a), under CA-02872 Zimmer Biomet will determine the proper [redacted] per cleanroom in compliance with ISO 14644 and will update procedures accordingly.

Zimmer Biomet trained personnel to the requirements of the Interim Control and on the proper sampling technique (see attachment 2B-E, *IC-001 Training Records*). Following training of personnel, implementation of IC-001, and other actions implemented in connection with other Observations (e.g., the venting and qualification of [redacted] sealers), [redacted], and [redacted]). The other cleanrooms will be requalified using the requirements in ISO 14644-1:2015 once the required risk assessments are complete.

Zimmer Biomet achieved containment [redacted] until Zimmer Biomet completed the evaluation of Observation 2(B) [redacted] Additionally, [redacted] (b) (4) [redacted].

With respect to product in the field that was processed through one of the cleanrooms, Zimmer Biomet conducted a [redacted] review of [redacted] of microbial surface/air and particulate data from the cleanrooms (see attachment 2B-I, [redacted]). Zimmer Biomet has determined that [redacted]. Furthermore, [redacted], Zimmer Biomet determined that [redacted] Therefore, Zimmer Biomet has determined that [redacted] In addition, Zimmer Biomet has initiated a Health Hazard Evaluation Determination to assess the potential impact to patients and whether there is a need to escalate the findings to a Health Hazard Evaluation ("HHE") (see attachment 2B-K, *HHED #12-2016-034*). [redacted]

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(b) (4) . HHE 2016-311 will be completed by (b) (4) . Zimmer Biomet will provide details regarding any decisions reached or actions taken as a result of the HHE in our update on (b) (4)

To identify an appropriate long-term solution to the environmental monitoring gaps for cleanrooms identified in Observation 2(B), Zimmer Biomet will thoroughly investigate the findings under CA-02965. Zimmer Biomet plans to: (1) review the relevant SOPs, Instructions, Quality Procedures, environmental drawings, sample locations, and data for environmental control of cleanrooms; (2) review the particle counters in cleanrooms for proper settings (b) (4) as needed; (3) perform a gap assessment of the documents and records in task (1) against the appropriate regulations, standards, and guidances; (4) evaluate the appropriate monitoring of the cleanrooms and work environment; (5) evaluate the process for assessing changes to the cleanrooms and work environments prior to implementing changes; and (6) evaluate product impact based on environmental excursions. Following the completion of these investigation steps, Zimmer Biomet will identify and implement appropriate corrective actions. Zimmer Biomet will provide details of and timelines for any such actions in future updates to this response.

CAPA CA-02872 / Observations 2(B)(iii), 2(B)(iv), and 2(B)(v)

Interim Control IC-001 also contains environmental control requirements for WEs. Sections 7.1.4, 7.3, 7.2, and 7.2.3.2 of IC-001 contain methods for increased environmental monitoring, change control, excursion investigation and escalation for WEs, in addition to cleanrooms. Personnel have been trained to all elements of IC-001, including those applicable to WEs.

(b) (4)

In addition, Zimmer Biomet promptly implemented several corrections to address the findings regarding environmental control of WEs contained in Observations 2(B)(iii). (b) (4) , (b) (4) (see attachment 2B-L, Cleaning Work Orders). Zimmer Biomet implemented (b) (4) cleaning schedule to ensure the vents are maintained in a clean state free of debris and dust). Further, Zimmer Biomet will report further improvements in subsequent updates to the Agency.

With respect to excursions in WEs identified in Observation 2(B)(iv), IC-001 will ensure that any similar excursions are properly evaluated and escalated when appropriate. Further, Zimmer Biomet has evaluated the WE excursions identified in Observation 2(B)(iv) in HHED 12-2016-034 (see attachment 2B-K). The determination reached in (b) (4)

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(b) (4) is still in progress. HHE 2016-311 will be completed by (b) (4). Zimmer Biomet will provide details regarding any decisions reached or actions taken as a result of the HHE in our update on (b) (4).

Finally, with respect to the inconsistent environmental control requirements (b) (4)) identified in Observation 2(B)(v), Zimmer Biomet will review the potential product or patient impact under HHED 12-2016-034

In addition to the containment actions and corrections identified above, Zimmer Biomet will complete an investigation under CAPA CA-02872 to evaluate and identify appropriate long-term corrective actions. Zimmer Biomet intends to: (1) review the relevant SOPs, Instructions, Quality Procedures, and data for the faculties, processes, and procedures for environmental control of WEs ,CEs, and cleanrooms; (2) observe the staff performing the procedures identified in step (1) to determine compliance with the established procedures; (3) perform a gap assessment of documents and records identified in step (1) against the appropriate regulations, standards, and guidance documents; (4) perform a walkthrough of WEs, CEs, and cleanrooms to determine if the defined area is adequate for the intended use; and (5) perform a walkthrough of WEs, CEs, and cleanrooms to determine if the design and layout are appropriate for the intended use. Zimmer Biomet will provide details of and timelines for any such actions in future updates to this response.

Completed Actions:

No.	Action	Completion Date
2B-1	Initiated CAPA CA-02872 to address the issues identified in Observations 2(B)(iii, 2(B)(iv), and 2(B)(v) (see attachment 2B-B).	September 21, 2016
2B-2	(b) (4) (b) (4)	September 28, 2016
2B-3	(b) (4)	September 29, 2016
2B-4	(b) (4)	October 12, 2016
2B-5	Initiated HHED #12-2016-034 to assess the potential impact to patients (see attachment 2B-K).	October 13, 2016
2B-6	Conducted a walkthrough of WEs, CEs, and cleanrooms to determine if the defined areas are adequate for their intended use.	October 14, 2016
2B-7	Conducted a walkthrough of WEs, CEs, and cleanrooms to determine if the design and layout are appropriate for their intended use.	October 14, 2016
2B-8	Initiated CAPA CA-2965 to address the issues identified in Observations 2(B)(i) and 2(B)(ii) (see attachment 2B-A).	October 14, 2016
2B-9	Review the particle counters in cleanrooms for proper settings and (b) (4) as needed.	October 15, 2016

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2B-10	Trained personnel to the requirements of IC-001, Rev. 2 (see attachment 2B-E)	December 14,2016
2B-11	Revised drawings in cleanroom instructions ("INSTs") to provide a clear definition of particulate counting locations (see attachment 2B-D)	November 11 and 15, 2016
2B-12	Determined that particulate alert and action limits and microbial air levels in cleanrooms in (b) (4) (b) (4) (see attachment 2B-J)	October 27, 2016
2B-13	Instituted Interim Control IC-001 to govern environmental controls (see attachment 2B-C).	October 28, 2016
2B-14	Requalified the (b) (4) cleanroom ((b) (4)) and (b) (4) l cleanroom ((b) (4) (b) (4)) (see attachments 2B-F and 2B-G).	October 5-19, 2016 and October 5-30, 2016
2B-15	Conducted an initial (b) (4) review (b) (4) of data from the cleanrooms (see attachment 2B-M).	October 31, 2016
2B-16	Evaluated product impact based on environmental excursions. (see attachments 2B-N and 2B-O)	November 2, 2016
2B-17	Initiated HHE # 2016-311 to evaluate the potential product and safety impact of the findings in Observation 2(B).	December 15, 2016

Planned Actions:

No.	Action	Completion Date
2B-18	Complete HHE 2016-311 to determine the risks associated with gowning area and work environment issues and the actions, if any, Zimmer Biomet should take to resolve them.	(b) (4)
2B-19	Review relevant SOPs, Instructions, Quality Procedures, environmental drawings, sample locations, and data for environmental control of cleanrooms and WEs.	(b) (4)
2B-20	Implement (b) (4) cleaning schedule for vents in WEs	(b) (4)
2B-21	Perform a gap assessment of the documents and records against the appropriate regulations, standards, and guidances.	(b) (4)
2B-22	Perform a gap assessment of documents and records regarding environmental control of WEs, CEs, and cleanrooms against the appropriate regulations, standards, and guidance documents.	(b) (4)
2B-23	Evaluate product impact based on environmental excursions, through completion of HHE process initiated on December 15, 2016.	(b) (4)
2B-24	Observe the staff performing the procedures for environmental control of WEs, CEs, and cleanrooms to determine compliance with the established procedures.	(b) (4)
2B-25	Complete CA-02872 Root Cause/Action Plan Phase.	(b) (4)
2B-26	Complete CA-02965 Root Cause/Action Plan Phase.	(b) (4)

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2B-27	Complete CA-02872 Implementation Phase.	Target completion date to be reported in a future update
2B-28	Complete CA-02965 Implementation Phase.	Target completion date to be reported in a future update
2B-29	Verify effectiveness of CA-02872 and close CAPA.	Target completion date to be reported in a future update
2B-30	Verify effectiveness of CA-02965 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation 3

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FDA Observation #3(A)

Specifically,

A. **Procedure *QM 13.0: Control of Nonconforming Product* (Rev. 8, effective 8/7/2014 to 9/18/2016) does not ensure that nonconforming product is consistently identified, documented, and evaluated to determine the need for an investigation. Specifically, per Sections 7.3.1 and 7.3.2,** [redacted]

Observation 3(A) Investigation and Response:

Earlier this year, Zimmer Biomet [redacted]. In May 2016, Zimmer Biomet initiated [redacted] June 24, 2016, Zimmer Biomet initiated CAPA CA-02645 to address nonconforming product issues [redacted] (see attachment 3A-A, *CAPA CA-02645 Summary*). At the time of the FDA inspection, CAPA CA-02645 was in the Investigation (Root Cause/Action Plan) Phase. After the inspection, on November 22, 2016, Zimmer Biomet expanded the scope of CAPA CA-02645 to address system-wide issues concerning control of product that does not conform to specified requirements.

Prior to the inspection, on June 2, 2016, as a part of the issue review phase of CAPA CA-02645, Zimmer Biomet revised SOP 13.0.1 to allow for appropriate deviation dispositions by requiring [redacted] (see attachment 3A-B, *SOP 13.0.1 Deviation Procedure* (Rev. 14)). There were additional updates to SOP 13.0.1 to provide procedure guidance and to provide greater control over nonconforming [redacted] As additional improvement, Zimmer Biomet implemented an electronic nonconforming material process called [redacted]. This new [redacted] application was fully implemented on [redacted]. In connection with the planned implementation of [redacted], Zimmer Biomet updated SOP 13.0.1 on November 11, 2016 (see attachment 3A-C, *SOP 13.0.1 Nonconforming Product Procedure* (Rev.

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17)). Zimmer Biomet conducted classroom training of relevant personnel on SOP 13.0.1 (Rev. 17) during (b) (4) (see attachment 3A-D, (b) (4)(b) (4)).

On December 15, 2016, 2016, Zimmer Biomet implemented an interim control to address the (b) (4) ((b) (4))(b) (4)). The term (b) (4) has been stricken from IC-034 and, per the interim control, whenever there is (b) (4) . On December 16, 2016, Zimmer Biomet trained appropriate personnel to the requirements of IC-034 (see attachment 3A-F, *IC-034 Training Records*).

Pursuant to CAPA CA-02645, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 3(A); and
2. Assess current (b) (4) procedure, practice, and documentation and determine process gaps.

In addition, Zimmer Biomet will conduct a system-wide investigation of its procedures for controlling product that does not conform to specified requirements.

Completed Actions:

No.	Action	Completion Date
3A-1	Initiated CAPA CA-02645 to address nonconforming product issues (see attachment 3A-A).	June 24, 2016
3A-2	Revised SOP 13.0.1 to allow for appropriate deviation dispositions[(b) (4)] (see attachment 3A-B).	June 2, 2016
3A-3	Updated SOP 13.0.1 in connection with rollout of (b) (4) (see attachment 3A-C).	November 11, 2016
3A-4	Conducted classroom training of relevant personnel on SOP 13.0.1 revisions (see attachment 3A-D).	November 11-December 12, 2016
3A-5	Expanded CAPA CA-02645 to investigate system-wide procedures for controlling product that does not conform to specified requirements (see attachment 3A-A).	November 22, 2016
3A-6	Implemented an interim control to address the (b) (4) (b) (4) (see	December 15, 2015

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	attachment 3A-E).	
3A-7	Trained appropriate personnel to the requirements of IC-034 (see attachment 3A-F).	December 16, 2016
3A-8	Completed CAPA CA-02645 Correction Phase.	December 14, 2016

Planned Actions:

No.	Action	Completion Date
3A-9	Complete root-cause analysis of the issues identified in Observation 3(A).	(b) (4)
3A-10	Assess current (b) (4) , practice, and documentation.	(b) (4)
3A-11	Complete CAPA CA-02645 Investigation (Root Cause/Action Plan) Phase.	Target completion date to be reported in a future update
3A-12	Complete CAPA CA-02645 Implementation Phase.	Target completion date to be reported in a future update
3A-13	Verify effectiveness of CAPA CA-02645 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #3(B)

B. Nonconforming product is not routinely documented using your firm's *Product Deviation/Reject Reports*. For example:

i. On 09/13/2016, a Packager responsible for packaging devices in the Sports Medicine Department of the Cleanroom) explained that employees use spreadsheets to document repackaging (*i.e.*, rework) activities required to address failed visual inspections. The spreadsheets are uncontrolled and their use is not defined by any quality system procedure as of 9/13/2016. As shown by the table below, approximately % more failed visual inspections have been documented using the uncontrolled spreadsheets than on *Product Deviation/Reject Reports*:

Documentation	Date Range	Number of Nonconformances
Product Deviation/Reject Reports **initiated for (b) (4) (Packaging Seal Area—Under-Sealed, Over-Sealed, or Wrinkles/Folding/Cracks)**	**7/1/2014—9/13/2016 (805 calendar days)**	**420**
Uncontrolled spreadsheets indicating packages with "wrinkle" and/or "bad seal" defects	**4/29/2016—9/13/2016 (137 calendar days)***	**1,597**

*** As of 9/15/2016, only 48 days of uncontrolled spreadsheet data in this date range had been maintained and available for our review**

Notably, the uncontrolled spreadsheets are only used in the Sports Medicine Department of cleanroom , as stated by the Manufacturing Supervisor of that area on 9/13/2016. Between 7/1/2014 and 9/9/2016, only % of all devices packaged in were done so in the Sports Medicine Department of cleanroom devices).

ii. Outside of the Sports Medicine Department in , interviews with operators from several areas throughout revealed additional instances of nonconforming product not routinely being documented as deviations. For example:

i. In the Cleanroom, Final Packaging Operators in the Poly Departments cited incomplete seals or particles within the packaging.

ii. **In the [redacted] Work Environment Cleaning Operators cited knee femoral implants found notably soiled after passing through the [redacted] ultrasonic cleaner.**
iii. **In the [redacted] Cleaning inspection Work Environment Cleaning Operators cited parts that are still soiled after performing validated cleaning operations.**
iv. **In the [redacted], Machining Operators cited hip stem tapers that do not meet specification.**
v. **In the [redacted] Area, [redacted] Inspection Operators cited bars with areas of perceived unconsolidation or inherent defects.**

Observation 3(B) Investigation and Response:

[redacted], Zimmer Biomet initiated CAPA CA-02645 to address nonconforming product issues [redacted]. At the time of the FDA inspection, CAPA CA-02645 was in the investigation phase. After the inspection, on November 22, 2016, Zimmer Biomet expanded the scope of CAPA CA-02645 to address system-wide issues concerning control of product that does not conform to specified requirements.

To address the packaging issue in which uncontrolled documents were found to record failed visual inspection; on December 15, 2016, 2016, Zimmer Biomet implemented an interim control to address the [redacted] as nonconforming product ([redacted]). Any inspection that does not meet the criteria will require a Nonconformance Report ("NCR"). Zimmer Biomet verified per procedure CP05100 (rev 2) Good Documentation Practices (see attachment 3B-A Good Documentation Practices) that the use of uncontrolled documents is prohibited. A plant wide communication was made on the prohibited use of uncontrolled documentation per CP05100. Additionally, a review was performed of the manufacturing facility to ensure there were no uncontrolled forms currently in use.

To address the examples listed in Observation 3(B) of failures to document nonconforming product appropriately (i.e., on *Product Deviation/Reject Reports* (form INST 13.0.1.1)), Zimmer Biomet will review good documentation practices and document control procedures and verify that uncontrolled documents are prohibited. In addition, Zimmer Biomet will:

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1. In the (b) (4) Department, review final packaging and determine whether inspection documents include incomplete seals or particles within the packaging and update documentation as necessary;
2. In the (b) (4) Work Environment, verify that part cleanliness criteria are documented after passing through the (b) (4) cleaner and update documentation as necessary;
3. In the (b) (4) Work Environment, verify that part cleanliness criteria are evaluated after performing validated cleaning operations and update documentation as necessary;
4. In the (b) (4), verify that pass/fail criteria for (b) (4) are included in the documentation and update documentation as necessary; and
5. In the (b) (4) Area, review (b) (4) and verify that pass/fail criteria is included for ultra-high molecular weight polyethylene bars with areas of perceived unconsolidation or inherent defects.

Pursuant to CAPA CA-02645, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 3(A); and
2. Assess current procedure, practice, and documentation relating to documentation of nonconforming product and determine process gaps.

In addition, as stated previously, Zimmer Biomet will conduct a system-wide investigation of its procedures for controlling product that does not conform to specified requirements.

Completed Actions:

No.	Action	Completion Date
3B-1	Initiated CAPA CA-02645 to address nonconforming product issues.	24 June 2016
3B-2	Revised CAPA CA-02645 to investigate system-wide procedures for controlling product that does not conform to specified requirements.	22 November 2016
3B-3	Completed CAPA CA-02645 Correction Phase.	December 14,2016
3B-4	Zimmer Biomet verified per procedure CP05100 (rev 2) Good Documentation Practices (see attachment 3B-A) that the use of uncontrolled documents is prohibited. A plant wide communication was made on the prohibited use of uncontrolled documentation per CP05100.	June 29, 2016

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No.	Action	Completion Date
3B-5	Complete root-cause analysis of the issues identified in Observation 3(B).	(b) (4)
3B-6	Complete CAPA CA-02645 Investigation (Root Cause/Action Plan) Phase.	Target completion date to be reported in a future update
3B-7	Complete CAPA CA-02645 Implementation Phase.	Target completion date to be reported in a future update
3B-8	Verify effectiveness of CAPA CA-02645 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #3C

C. Since 2/8/2012, 4 routine loads sterilized by [redacted] sterilization [redacted] have failed biological indicator (BI) sterility testing. In 3 out of 4 instances, the nonconforming product comprising the loads was not evaluated to determine the need for an investigation. Specifically:

Load Number	Date of Confirmed BI Failure	Quantity of Lots	Quantity of Devices
01242-CC	2/9/2012	[redacted]	[redacted]
10213-G	11/5/2013	[redacted]	[redacted]
11203-C	12/9/2013	[redacted]	[redacted]

In each case, the loads were resterilized as instructed by Revisions 4 and 5 of SOP 9.4.3 (effective 12/5/2007 and current as of 11/16/20 16) and subsequently distributed. Notably, the BIs tested during routine sterilization are located on the outside of the [redacted] totes containing product as described in Observation 1, Part B.

The fourth BI sterility testing failure since 2/8/2012 was confirmed on 9/12/2016 (Load Number 08296-C). Issue Evaluation #IE-000387 was initiated during this inspection on 9/13/2016 to investigate the failure.

Observation 3C Investigation and Response:

During the inspection, on September 19, 2016, Zimmer Biomet opened CAPA CA-02867 to investigate and address a positive biological indicator ("BI") result that occurred during a routine sterilization run of [redacted] and Sports Medicine products (see attachment 3C-A-CA-02867). Following the conclusion of the inspection, the findings of Observation 3(C) regarding the failure to evaluate or investigate three runs with failed BIs and the resulting nonconforming products from these three runs were added to CA-02867. CA-02867 is in the Investigation (Root Cause/Action Plan) Phase.

Observation 3(C) documents the occurrence of four BI (Biological Indicator) failures in routine sterilization loads of [redacted] and Sports Medicine products sterilized by [redacted] ([redacted]) sterilization [redacted] Three of the failures noted in the

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Observation occurred between 2012 and 2013. For these three historical failures, the loads were resterilized and released per the then-current procedure (SOP 9.4.3, [redacted] rev. 4 and rev. 5), which allowed resterilization of the load when a positive BI occurred. At the time of the historical failures, there was no requirement to document the failure as part of the non-conforming material process and as such, no investigation was performed. This historical practice did not conform to [redacted], which specified in sections 11.1 through 11.3, that product shall be considered as non-conforming and handled in accordance with applicable requirements of ISO-13485 in the event of a positive BI. [redacted] also required that the cause of a positive BI shall be investigated. As an initial correction under CAPA CA-02867, Zimmer Biomet revised SOP 9.4.3 on December 15, 2016 to [redacted], per Section 7.3 (see attachment 3C-B-SOP 9.4.3.). Additionally, Zimmer Biomet removed the section of SOP 9.4.3 that [redacted]

The fourth and most recent BI failure occurred on September 2, 2016. [redacted]) (see attachment 3C-C-PBI#0498). Zimmer Biomet immediately generated a Product Deviation Report (see attachment 3C-D-Product Deviation Report 09-13-2016) and opened an Issue Evaluation, IE-00387, on September 13, 2016, as acknowledged in the Observation (see attachment 3C-E-IE-00387.). The product in this non-conforming sterile load [redacted]

In addition to [redacted] Zimmer Biomet also [redacted].

Products which were resterilized after the 3 previous BI failures will be investigated as part the Investigation (Root Cause/Action Plan) Phase of CAPA- 02867. Zimmer Biomet will determine through the investigation whether any additional actions, such as field actions, are necessary and will provide information about any such actions in future updates to this response.

Revisions to the non-conforming product quality system across the Warsaw North Campus and related system-wide corrective actions will proceed under CAPA CA-02465, as discussed in the response to Observation 3.

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Completed Actions:

No.	Action	Completion Date
3C-1	(b) (4)	September 12, 2016
3C-2	Opened IE-00387 to investigate the positive BI result for Load #08296-C (see attachment 3C-E).	September 13, 2016
3C-3	Initiated CAPA CA-02867 to address the issues identified in Observation 3(C) regarding the lack of investigation of positive BI results and the resulting non-conforming product (see attachment 3C-A).	September 19, 2016
3C-4	Implemented (b) (4) (b) (4) (b) (4) (b) (4) Cycle (see attachment 3C-F).	September 20, 2016
3C-5	Updated SOP 9.4.3 to indicate that product shall be considered as nonconforming in the event of a positive BI result and that the cause of the positive BI result shall be investigated, in order to align this procedure with the requirements of (b) (4) (see attachment 3C-B).	December 16, 2016

Planned Actions:

No.	Action	Completion Date
3C-6	Review product shelf life/stability data to determine if there is data to support greater than (b) (4) sterilization as part of the investigation of the three positive BI results in 2012 and 2013, identified in this Observation. This review will also include products that are sterilized (b) (4). This action is also documented in the response to Observation 1B and will be completed as part of CAPA CA-02867.	(b) (4)
3C-7	Conduct an HHED/HHE to address the (b) (4) sterilized products that are in the field that received (b) (4) (b) (4) sterilization without supporting data, if applicable. This action is also documented in the response to Observation 1B and will be completed as part of CAPA CA-02867.	(b) (4)
3C-8	Complete CAPA-02867 Root Cause and Action Plan Phase	(b) (4)
3C-9	Complete CAPA-02867 Implementation Phase	Target completion date to be reported in a future update
3C-10	Verify Effectiveness of CAPA-02867 and Close CAPA	Target completion date to be reported in a future update

FDA Observation #3(D)

D. Procedures governing the placement of devices on quality hold and their removal have not been documented. Your firm's Quality Director explained that quality holds are used to prevent shipment of nonconforming product in inventory and under your firm's control. Your firm's ERP transaction history indicates 10,129 quality hold transactions and 4,099 release transactions since 7/1/2014. We sampled 15 release transactions and observed that:

i. For 11 of the 15 release transactions, your firm was unable to provide documentation showing the detailed reason for the quality hold, reason and approval of its release, or the lot numbers within the scope of the hold/release.

ii. For 3 of the 15 release transactions, your firm was able to provide emails requesting the holds and the product scopes; however, the detailed reason for the quality hold was not documented. Additionally, the reason or approval for releasing these quality holds was not documented.

iii. For 1 of the 15 release transactions, your firm was able to provide an email requesting part and lot numbers to be released from quality hold. However, your firm was unable to provide documentation showing approval of the release.

Observation 3(D) Investigation and Response:

Quality holds are used to prevent shipment of nonconforming or suspected nonconforming material that is in inventory. During the recent inspection, on September 19, 2016, Zimmer Biomet initiated CAPA CA-02864 to address the lack of procedures governing the placement of devices on quality hold and their removal (see attachment 3D-A, *CAPA CA-02864 Summary*). This lack of documentation resulted in the inability to assure a consistent process for defining the reason for the hold; hold instructions, including containment; hold notifications; product disposition; and hold approval. In addition, consistent scoping and approval of items/lots to be placed on or released from hold, and documentation of the scope reconciliation, were not in place.

On September 26, 2016, Zimmer Biomet's Warsaw North Campus created, trained-on, and implemented a documented hold process (see attachment 3D-B, *SOP 13.0.2 Placing Finished Goods Inventory On Hold*, and attachment 3D-C, *SOP 13.0.2 Training Record*). This newly

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deployed process leveraged the product hold process that exists at the (b) (4) . The recently implemented quality hold process and examples were provided to the investigators during the FDA Inspection. Examples of the quality hold process can be found in attachments to many of the responses to the observation. This formalized the quality hold process at the Warsaw North Campus and required Warsaw North Campus personnel to:

1. Document communication of nonconforming product information and instructions for containment of the affected product and subsequent disposition (e.g., release, scrap, etc.) and close-out of the hold event.
2. Obtain written approval (b) (4) to initiate or modify a quality hold, including disposition and close-out; and
3. Include a scope list of the specific items/lots impacted by the nonconformance along with documented reconciliation of the selected items/lots. Note that if the scope changes (additions or removals) a new scope form and a revised and approved Hold Notification Form are required so as to identify and document the change.

Zimmer Biomet implemented the process at the Warsaw North Campus on a go-forward basis. The first quality hold implemented with the enhanced documentation was Quality Hold 2016-50. All new product holds and revisions to existing product holds will follow the enhanced product hold documentation requirements.

Pursuant to CAPA CA-02864, Zimmer Biomet will conduct a root-cause investigation that includes, but is not limited to, the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 3(D);
2. Review all quality holds in place prior to the implementation of SOP 13.0.2 to determine further actions;
3. Develop an implementation plan for CAPA CA-02864; and
4. Develop a verification of effectiveness ("VoE") plan for CAPA CA-02864.

Completed Actions:

Action Number	Action	Completion Date
3D-1	Initiated CAPA CA-02864 to address the issues identified in Observation 3(D) (see attachment 3D-A).	September 19, 2016

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3D-2	Implemented and trained Warsaw West Campus personnel on quality hold procedure (see attachment 3D-B and attachment 3D-C).	September 26, 2016

Planned Actions:

Action Number	Action	Completion Date
3D-3	Complete root-cause analysis of the issues identified in Observation 3(D).	(b) (4)
3D-4	Review the existing regulatory hold process and identify gaps.	(b) (4)
3D-5	Review all quality holds in place prior to the implementation of SOP 13.0.2 to determine further actions	(b) (4)
3D-6	Complete CAPA CA-02864 Investigation (Root Cause/Action Plan) Phase	(b) (4)
3D-7	Complete CAPA CA-02864 Implementation Phase.	Target completion date to be reported in a future update
3D-8	Verify effectiveness of CAPA CA-02864 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #3E

E. Devices manufactured using equipment operating under "run at risk" conditions are not adequately controlled. Such conditions are documented on forms INST 5.0.3.3, which SOP 5.0.3 (Rev. 8, effective 2/8/2016) states are used to "communicate validated specification changes for use during the manufacture of product while effected documents are revised." According to your firm's Associate Director of Manufacturing Engineering, devices manufactured under run-at-risk conditions are to be quarantined until the specification changes have been approved; however, this requirement has not been documented within a procedure.

We reviewed 1 of the 6 run-at-risk forms initiated since 1/1/2016, which pertained to pouch sealer [redacted] (Run-at-Risk #2016-003, effective 5/2/2016 to 7/2/2016). [redacted] relevant lots were packaged between 5/2/2016 and 7/2/2016, of which 9 were distributed prior to approval of the manufacturing specification changes on 06/30/2016. The 9 distributed lots were of Optipac bone cement monomer in 15 mL, 18 mL, and 20 mL sizes.

Observation 3E Investigation and Response:

On September 25, 2016, Zimmer Biomet opened CAPA CA-02893 to investigate and address the finding in Observation 3(E) concerning the use of equipment operating under run-at-risk conditions and the inadequate control of product manufactured under such conditions (see attachment 3E-A, *CA-02893 CAPA Summary*). CA-02893 is currently in the Root Cause/Action Plan Phase.

Zimmer Biomet investigated the history and use of the Run at Risk process and [redacted]

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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The Run at Risk process was also used as a temporary pathway for communication and implementation of validated specification changes prior to the formal release of updated specifications and related documents.

During the inspection, Zimmer Biomet implemented several immediate corrections to stop the use of the Run at Risk process. On September 26, 2016, Zimmer Biomet obsoleted the form used to implement Run at Risk activities, INST 5.0.3.3, *Run At Risk (R.A.R.) Form*, Rev. 4 (see attachment 3E-B,). On September 28, 2016, Zimmer Biomet removed references to the Run at Risk process (b) (4)). Zimmer Biomet trained relevant personnel on the changes to the procedures (see attachment 3E-G, *Training Records*).

Revision 8 of SOP 5.0.3*, Guidelines for the Use of Communication Memorandum and Posting of Instructions*, implemented on February 8, 2016, established a requirement to maintain a Run at Risk Log ("RAR Log") for all open and closed Run at Risk records. As a containment action during the inspection, Zimmer Biomet conducted a review of the RAR Log, which listed Run at Risks, including Run at Risk #2016-003 identified in Observation 3(E), all of which were closed at the time of the review. For each of the instances, which all related to the use of equipment while a completed validation was being finalized and procedures were being updated, Zimmer Biomet assessed: (1) the reason for using the Run at Risk process; (2) whether product was quarantined during the Run at Risk period; (3) the outcome of the Run at Risk activity (e.g., validation reports were completed or procedures were updated); and (4) the containment determination at the time of the Run at Risk activity. As a result of this assessment, . Further, for Run-at-Risk #2016-003 identified in the Observation, Zimmer Biomet determined

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(b) (4) As part of the investigation to be conducted under CAPA CA-02893, Zimmer Biomet will evaluate other historical instances of Run at Risk activity and determine if additional containment or corrective actions are needed.

(b) (4) Following the completion of the root cause assessment and the Investigation (Root Cause/Action Plan) Phase of CAPA CA-02893, Zimmer Biomet plans to revise relevant procedures for equipment to require that equipment not be released to production or, if already released to production, not be used if qualification activities are not completed, preventive maintenance is not completed on time, or validation and procedural updates are not completed. The details regarding these planned actions will be determined prior to the Implementation Phase of CA-02893 and Zimmer Biomet will provide further information regarding these corrective actions in future update responses.

Completed Actions:

No.	Action	Completion Date
3E-1	Initiated CAPA CA-02893 to address the issues identified in Observation 3(E) (see attachment 3E-A).	September 25, 2016
3E-2	Obsoleted INST, 5.0.3.3, *Run At Risk (R.A.R.) Form*, Rev.4 (see attachment 3E-B).	September 26, 2016
3E-3	Revised sections 3.3.4, 4.6, and 12.0 of SOP 5.0.3, (b) (4)	September 28,2016
3E-4	Revised sections 3.3.1, 7.1.8, and 7.2 of QM 9.7, (b) (4) (see attachment 3E-D).	September 28,2016
3E-5	Revised sections (b) (4) of SOP 9.2.1, (b) (4) (see attachment 3E-E).	September 28,2016
3E-6	Revised sections 3.3.12 and 9.3 of QM 9.4, (b) (4) see attachment 3E-F).	December 5, 2016
3E-7	Trained personnel to revised procedures (see attachment 3E-	December

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	G).	13, 2016
3E-8	Reviewed and assessed RAR Log to determine whether containment action was required for any of the six RAR instances on the log (see attachment 3E-H).	December 13, 2016

Planned Actions:

No.	Action	Completion Date
3E-9	Complete root cause and action plan phase for CA-02893.	(b) (4)
3E-10	Perform a (b) (4) review of Run at Risks (b) (4) to establishment of the RAR Log on (b) (4) .	(b) (4)
3E-11	Complete CA-02893 Implementation Phase.	Target completion date to be reported in a future update
3E-12	Verify effectiveness of CA-02893 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #3F

F. Devices packaged using sealers operating outside of a validated state are not documented as nonconforming product. For example:

i. Quality Alert #545 was initiated 3/10/2016 and instructed operators to begin documenting actual parameter settings used when operating sealer (b) (4). Of the (b) (4) lots ((b) (4) devices) packaged using sealer (b) (4) between 3/10/2016 and 9/27/2016, 31 lots were sealed using out-of-specification parameter settings and not documented as nonconforming product. 25 of the 31 lots (total of (b) (4) devices) (e.g., Vanguard knee tibial bearings with part numbers 183710, 183748, 183908, 183922, and 189708) had been distributed at the time of this inspection.

ii. *Package Sealer Increased Monitoring Protocol* (Rev 0, 08/19/2016), currently refered to as *IC09 Interim Control Sterile Packaging Sealer Increased Monitoring Interim Control,* (Rev 2, 11/15/2016) was approved on 8/19/2016 to begin documenting parameter settings used when operating all packaging sealers. The protocol instructs operators to document such parameters using *Manufacturing Process Form (MPF #0089.* As of 9/27/2016, the form had been implemented for (b) (4) sealers and your firm's PMO Manager stated that implementation for all other sealers was "almost completed." We reviewed one MPF#0089 form applicable to each of the (b) (4) sealers. 1 of the (b) (4) forms indicated that on 9/24/2016, Sealer (b) (4) was operating outside of the parameter ranges specified by *Process Engineering Specification 1. 31* (Rev. 91., effective 9/20/2016). The (b) (4) lots sealed on 9/24/2016 were not documented as nonconforming product.

Upon further review of all MPF #0089 forms by your firm during this inspection, 102 lots were sealed using out-of-specification parameter settings between 9/8/2016 and 9/27/2016 and not documented as nonconforming product. At least 43 of the 102 lots (total of (b) (4) devices) (e.g., Vanguard knee tibial bearings with item number 183724, tibial plates with item number

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814133002, and Jogger-Joe sports medicine devices with item number 110010372) had been distributed at the time of this inspection.

Observation 3F Investigation and Response:

(b) (4)

(b) (4)

. In response to the FDA inspection, the findings contained in Observation 3(F) were added to CAPA CA-02380 which is currently in the Investigation (Root Cause/Action Plan) Phase. CA-02380 will also investigate and address the findings in Observations 1(C) and 6(A).

On March 10, 2016, sealer operators were instructed via *Quality Alert #545* to begin documenting actual parameter settings when using Sealer (b) (4) . A Sealer (b) (4) quality log was introduced for operators to record the actual sealing parameter for the sealer with a supervisor or designee approval. This requirement was expanded to all sealers through *Package Sealer Increased Monitoring Protocol*, Rev. 0, effective on August 23, 2016. This protocol was later transferred to an Interim Control document IC-019, *Sterile Packaging Sealer Increased Monitoring Interim Control*, Rev. 1 on November 4, 2016 (see attachment 3F-B, *IC-019*). Please note that the Observation refers to this Interim Control with the incorrect number (IC-019 was incorrectly identified as IC09). Under the protocol and now the IC-019 requirements, operators document sealer parameter settings on Manufacturing Process Form MPF #0088, (b) (4) . Note that MPF 0088 replaced the Sealer (b) (4) quality log, which was no longer used after November 4, 2016. Between August 23 and November 4, 2016 the Sealer (b) (4) quality log and MPF 0088 were used in conjunction.

During the inspection, Zimmer Biomet implemented a general work instruction document, WIG 0234, *Sealer Interim Control, Product Release Procedure*, October 20, 2016 (see attachment 3F-C, *WIG 0234*). This WIG 0234 requirement was also a part of the initial release of IC 019 on November 4, 2016. Further, CAPA CA-02645 was opened to address the failure to adhere to the nonconforming product procedures, QM 13.0, *Control of Nonconforming Product*, and SOP 13.0.1, *Nonconforming Product Procedure*. CA-02645 will address any inconsistencies and deficiencies in the documentation and disposition of nonconforming products, as well as, to ensure that the dispositions are adequate and correct. This CAPA is discussed further in the separate response Observation 3(A).

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In response to this Observation, Zimmer Biomet took several product containment steps to ensure that only product that meets specification is distributed to the field. Specifically, in response to Observation 3F(i), Zimmer Biomet investigated the (b) (4) lots that were identified as orders sealed using out-of-specification parameter settings on Sealer (b) (4) . Based on this review, (b) (4) As part of ongoing containment for CAPA CA-02380, Zimmer Biomet will continue to review MPF 0088 and MPF 0089 forms to determine if additional nonconforming product reports (NCRs) or containment actions are required.

In response to the finding in Observation 3(F)(ii), Zimmer Biomet reviewed and investigated the MPF 0088 and MPF 0089 completed for Sealer (b) (4) on (b) (4) . As an immediate correction on November 23, 2016, Zimmer Biomet opened NCR #12127100 for the (b) (4) lots of product sealed on September 24, 2016 using Sealer (b) (4) (see attachment 3F-G, *NCR 12127100*). During the NCR investigation, Zimmer Biomet determined (b) (4) (b) (4) . (b) (4) . Following the completed NCR investigation on December 1, 2016, Zimmer Biomet (b) (4) (b) (4) (b) (4) .

Upon investigation of the finding in Observation 3(F)(ii) regarding MPF 0088 forms (incorrectly identified as MPF 0089 in Observation 3F) that contain manufacturing orders produced using sealer parameters that were out of specification, Zimmer Biomet identified a total of (b) (4) affected lots. This total includes the (b) (4) lots identified in Observation 3(F)(ii) as well as (b) (4) additional lots identified during the investigation. Zimmer Biomet has confirmed (b) (4) (b) (4) (b) (4) (b) (4) and documented in accordance with INST 13.0.2.3 (b) (4) Rev 3, effective December 6, 2016.

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Zimmer Biomet will continue to investigate the findings in Observations 3(F)(i) and 3(F)(ii) as part of CAPA CA-02380 to address the issue of operating the packaging sealers outside the process specification. In addition, under CAPA CA-02645, Zimmer Biomet will correct any inconsistencies in the documentation and disposition of nonconforming products and ensure the dispositions are adequate and correct. Process and procedural changes to ensure the appropriate use of the NCR process will also proceed under CA-02645, as described in the response to Observation 3(A).

Zimmer Biomet will continue to investigate the issues raised by the Investigators in Observation 3(F) and will identify appropriate corrective actions. Details of and timelines for any such actions will be included in future updates to this response. In addition, Zimmer Biomet is undertaking a site-wide review of the nonconforming product system, as described in the response to Observation 3. Updates on the progress of that effort will be provided in future update responses as well.

Completed Actions:

No.	Action	Completion Date
3F-1	Quality hold 16-061 (3F-D) initiated September 28, 2016	September 28, 2016
3F-2	Completed Health Hazard Evaluation Determination 09-2016-081 to determine the need for escalation to the Health Hazard Evaluation process (see attachment 3F-E).	October 5, 2016
3F-3	Implemented WIG 0234, *Sealer Interim Control, Product Release Procedure* required Quality review of MPF 0089 *Packaging Process Monitoring Log* and MPF 0088 (b) (4) (see attachment 3F-C).	October 20, 2016
3F-4	Initiated Interim Control IC 019, *Sterile Packaging Sealer Increased Monitoring Interim Control*, Rev. 1 (see attachment 3F-B).	November 4, 2016
3F-5	Initiated NCR #12127100 for orders sealed with out of specification settings on Sealer (b) (4) on September 24, 2016 (see attachments 3F-F and 3F-G).	November 23, 2016

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3F-6	Added findings from Observation 3(F) to existing CAPA CA-02380 regarding process validation and process monitoring of sealers (see attachment 3F-A).	December 14 2016

Planned Actions:

No.	Action	Completion Date
3F-7	Complete Investigation (Root Cause/Action Plan) Phase for CA-02380 for finding in Observation 3F (in addition to Observations 1C and 6A).	(b) (4)
3F-8	Conduct root cause analysis for CA-02380.	(b) (4)
3F-9	Complete CA-02380 Action Implementation Phase for finding in Observation 3F (in addition to Observations 1C and 6A), including: • Ongoing containment review, including, MPF forms and Sealer (b) (4) Quality Logs to determine if additional NCRs or containment actions are required • Investigate and complete Root Cause Analysis • Create action/implementation plan to address issues identified in Observation 3(F)	Target completion date to be reported in a future update
3F-10	Continue to review additional MPF forms and address any incorrect parameters through the NCR process	Ongoing per the current review process per WIG0234 and NCR process per SOP 13.0.1
3F-11	Verify effectiveness of CA-02380 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #3(G)

G. **Investigation and disposition documentation is not adequately reviewed and approved to ensure appropriate completion of all activities prior to releasing nonconforming product. For example, *Product Deviation/Reject Report* ("Deviation") #000245 was initiated on 6/3/2015 after (b) (4) bar stock lot (b) (4) processed in Vessel (b) (4) failed to meet specification for tensile strength as part of (b) (4) process monitoring performed under *QP0001: Manufactured Poly Bar* (b) (4) *Testing Requirements* (Rev. 10, effective 12/18/2014). Review of this deviation revealed:**

i. Testing performed during the investigation did not provide objective evidence that all bars in the lot met specifications. Your firm retested the tensile strength of the failed bar and (b) (4) bar in the (b) (4)-bar lot and released the lot after the retests met tensile strength specifications. Justification for accepting the entire lot of (b) (4) bars based on the test results of (b) (4) bars was not documented. Moreover, the deviation failed to provide evidence that tensile test samples were prepared from the core of the (b) (4) bars, which your firm's Associate Director of Biomaterials Research stated is the worst-case location with respect to material consolidation during the (b) (4) molding process.

ii. The "Investigation/Corrective Action" section of Deviation #000245 recommends to "Run full test on most recent lot produced from vessel (b) (4)" but this testing was never performed. As such, your firm was unable to provide objective evidence that the (b) (4) lots of (b) (4) bar stock manufactured in Vesse (b) (4) between 4/6/2015 (date the last lot that passed testing was processed) and 5/11/2015 (date the failed lot was processed) met specification for tensile strength. As of 10/20/2016, your firm distributed (b) (4) devices manufactured out of the (b) (4) lots of bar stock. Additionally, as of 9/9/2016, your firm distributed (b) (4) inches of the (b) (4) lots of bar stock to other Zimmer Biomet facilities for their manufacturing of finished devices.

Observation 3(G) Investigation and Response:

Zimmer Biomet uses an (b) (4) molding process to manufacture ultra-high molecular weight polyethylene (b) (4)) bar stock from (b) (4) . (b) (4) (b) (4) . (b) (4) Prior to the recent inspection,

Zimmer Biomet had been conducting (b) (4) process monitoring that consisted of at least (b) (4) sample from (b) (4) vessel used to produce (b) (4) bar stock.

During the inspection, on October 13, 2016, Zimmer Biomet (b) (4) (b) (4) process to address concerns regarding Zimmer Biomet's process monitoring. Then, on October 21, 2016, Zimmer Biomet conducted (b) (4) analysis of data related to the production of (b) (4) bar stock manufactured using both (b) (4) (b) (4) between January 2015 and July 2016. The (b) (4) analysis showed that the (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) This (b) (4) analysis also demonstrated (b) (4) .

Resin Type	Peak Stress (b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)

Figure 1. (b) (4))

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03077 to address the issues identified in Observation 3(G). CAPA CA-03077 is currently in the Investigation (Root Cause/Action Plan) Phase (see attachment 3G-B, *CAPA CA-03077 Summary*). Earlier, on June 24, 2016, Zimmer Biomet initiated CAPA CA-02645 ((b) (4)) to address system-wide issues concerning control of product that does not conform to specified requirements. CAPA CA-02645 also is in the Investigation (Root Cause/Action Plan) Phase.

On December 7, 2016, Zimmer Biomet initiated a Health Hazard Evaluation-Determination ("HHED") to determine the clinical impact, if any, on distributed products that were manufactured using (b) (4) bar stock produced in Vessel (b) (4) between April 6, 2015 (b) (4) (b) (4)) and May 11, 2015 (b) (4) (b) (4)) (see attachment 3G-C, *HHED 12-2016-016*). The HHED addressed (1) the (b) (4) distributed devices manufactured using the (b) (4) lots of (b) (4) bar stock produced in Vessel (b) (4) between April 6, 2015, and May 11, 2015, and (2) the (b) (4) inches of bar stock distributed to other (b) (4) that were manufactured using the same (b) (4) lots. The conclusion of the HHED assessment was (b) (4)

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H. During the inspection, on November 8, 2016, Zimmer Biomet implemented a standard operating procedure ("SOP") that applies to all validated processes at the Warsaw North Campus and defines the requirements for process monitoring of outputs of validated processes (see attachment 3G-D, *SOP 9.3.4 Process Monitoring of Validated Processes*). The SOP provides instructions for launching investigations when sample test results fall outside of specification or exhibit unexpected process trends and establishing and maintaining variable sampling and monitoring plans used to monitor the outputs of validated processes. Specifically, in the event that the sample mean or standard deviation falls outside of the defined Process Control Limit(s), or if the test results are out of specification, an investigation of the process is required. Finally, under SOP 9.3.4, all required testing must be completed, with results entered into the appropriate software system, and all required investigations must be completed and documented.

Earlier, on October 21, 2016, Zimmer Biomet implemented Interim Control IC-008 (see attachment 3G-E, *Interim Control IC-008*), which provides an increase to process monitoring of the process, and restarted the process on October 24, 2016. (b) (4) (b) (4) . (b) (4) In addition to the sampling above, morphology samples are being pulled from each of (b) (4) lots of (b) (4) bar stock manufactured for both (b) (4) ((b) (4) lots total) to estimate the standard deviation for each characteristic (b) (4) . Test samples for morphology will continue to be collected from (b) (4) selected bar from (b) (4) lot to establish a statistically based process monitoring sampling plan within QP0001. Zimmer Biomet trained appropriate personnel to the requirements of IC-008 (see attachment 3G-F, *IC-008 Training Records*).

Pursuant to CAPA CA-03077, Zimmer Biomet will conduct an investigation that includes the following tasks:

3. Characterize homogeneity within lot (b) (4)) for all bars produced to confirm the tested samples represent all remaining untested material within the same lot;
4. Develop a test protocol to quantify the statistical difference between vessel (b) (4) and all other vessels to confirm the (b) (4) test results will also apply to all other vessels;
5. Conduct a root-cause analysis of the failed (b) (4) test results identified in Observation 3(G);

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6. Conduct a root-cause analysis to determine why investigation and disposition documentation was not required prior to the release of nonconforming product; and
7. Reassess containment following the root-cause analyses and characterization of process homogeneity within lots and across vessels.

Pursuant to CAPA CA-02645 ((b) (4) Zimmer Biomet will conduct an investigation of its (b) (4)

Completed Actions:

No.	Action	Completion Date
3G-1	Implemented Interim Control IC-008 to increase to (b) (4) process monitoring of the (b) (4) process (see attachment 3G-E, *Interim Control IC-008*).	October 21, 2016
3G-2	Conducted (b) (4) analysis of the data related to the production of (b) (4) bar stock manufactured using both (b) (4) between January 2015 and July 2016, which showed (b) (4) (b) (4) (b) (4) (see attachment 3G-A, *ZRM_BI_0001_16 OOS Investigation for FDA 483 Observation 3G*).	October 21, 2016
3G-3	During the inspection, on November 8, 2016, Zimmer Biomet implemented a standard operating procedure ("SOP") that applies to all validated processes at the Warsaw North Campus and defines the requirements for process monitoring of outputs of validated processes (see attachment 3G-D). The SOP provides instructions for launching investigations when sample test results fall outside of specification or exhibit unexpected process trends and establishing and maintaining variable sampling and monitoring plans used to monitor the outputs of validated processes.	November 8, 2016

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3G-4	Trained appropriate personnel to the requirements of #IC-008 (see attachment 3G-F, *IC-008 Training Records).*	Various dates in November - December 2016
3G-5	Initiated CAPA CA-03077 to address the issues identified in Observation 3(G) (see attachment 3G-B, *CAPA CA-03077 Summary*).	December 1, 2016
3G-6	Initiated Health Hazard Evaluation Determination to determine the clinical impact, if any, of distributed products manufactured using (b) (4) bar stock produced in Vesse (b) (4) between (b) (4) (see attachment 3G-C, *HHED 12-2016-016*).	December 7, 2016

Planned Actions:

No.	Action	Completion Date
3G-7	Develop a test protocol to characterize homogeneity of within lot (b) (4)) for all bars produced to confirm the tested samples represent all remaining untested material within the same lot.	(b) (4)
3G-8	Develop a test protocol to quantify the statistical difference between vessel (b) (4) and all other vessels to confirm the (b) (4) test results will also apply to all other (b) (4).	(b) (4)
3G-9	Conduct root cause analysis to determine why investigation and disposition documentation was not required to release nonconforming product.	(b) (4)
3G-10	Conduct root cause analysis for the failed tensile test results identified in Observation 3(G).	(b) (4)
3G-11	Reassess containment following root cause analysis and characterization of process homogeneity within lots and across (b) (4)	(b) (4)
3G-12	Complete CA-03077 Investigation (Root Cause/Action Plan) Phase.	(b) (4)
3G-13	Complete CA-03077 Implementation Phase.	Target completion date to be reported in a

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		future update
3G-14	Verify effectiveness of CA-03077 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation 4

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FDA Observation #4

Procedures for design control have not been established.

Specifically,

The devices within the scope of DHF #KN152 (approved 2/3/2003) have not been designed in accordance with the requirements of 21 CFR 820.30. The product scope of DHF #KN152 includes (b) (4) item numbers (b) (4) implant item numbers and (b) (4) instrument item numbers):

- **Femoral components:**
  - **Vanguard Cruciate Retaining (CR) Interlok (b) (4) sizes)**
  - **Vanguard Posterior Stabilizing (PS) Interlok (b) (4) sizes)**
  - **Vanguard CR Porous Coat (b) (4) sizes)**
- **Tibial bearings:**
  - **Vanguard CR (b) (4) sizes)**
  - **Vanguard CR Lipped (b) (4) sizes)**
  - **Vanguard PS ((b) (4) sizes)**
- **Vanguard femoral distal augments (b) (4) sizes)**
- **Vanguard femoral posterior augments (b) (4) sizes)**
- **Instrumentation ((b) (4) item numbers)**

For example, the DHF indicates that:

A. **The design and development plan, *INST 4.0.1.1: Product Development Record* (dated 5/31/2001) does not:**

   i. **Define responsibility for implementation of the design and development activities.**
   ii. **Identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process.**

B. **It is unclear if or when all design input requirements were reviewed and approved during the design project. Your firm's Product Development Engineer explained that design inputs were approved during the first design review, which was held on 11/9/2001 and documented by *INST 4.0.3.1*. However, the "Design Inputs" section of the design review documentation indicates that design inputs had not been fully established at that time. For example, it states:**

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i. (b) (4) **Your firm was unable to explain when all other device components within the scope of this DHF began to be** (b) (4) **or when the associated inputs were reviewed and approved. Notably, PS femoral components comprise only** (b) (4) **of the implant item numbers (approximately** (b) (4)**) within the scope of the design project.**

ii. (b) (4) **Your firm's Development Director, Transformative Technology, Knees explained that the** (b) (4)

The documentation provides no objective evidence that implants other than PS femoral components were reviewed and approved during the initial design review.

Updated design inputs were documented in the "Design File Review Matrix" (approved 8/4/2003); however, this document post-dates the final approval of the design project for commercial release. The DHF contains no objective evidence to demonstrate that these design inputs were approved prior to commercial release.

C. Procedures to include a mechanism for addressing incomplete and/or ambiguous design input requirements have not been established. For example:

i. The DHF does not contain or reference documentation defining the intended use specific to the two types of femoral components (CR and PS) and three types of tibial bearings (CR, PS, and CR Lipped) within the scope of the design project. As such, design input requirements specific to each component type were not documented.

ii. The DHF does not contain design input requirements for use in revision surgeries. The indications for use shown in the current device package insert labeling (01-50-0975, Rev. M, effective 2015-03) include "Correction or revision of unsuccessful osteotomy, arthrodesis, or failure of previous joint replacement procedure."

iii. The design inputs as documented in the "Design File Review Matrix" (approved 8/4/2003) are incomplete and/or ambiguous. For example:

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a. Although it is listed as an "Input Requirement", the "Description" section in fact describes the design output of the femoral components, tibial bearings, and augments. For example, it describes femoral components as follows:

(b) (4)

b. Although it is listed as an "Input Requirement", the "Special Features(s) / Performance Characteristics" section indicates "same as predicate" and lists items such as the following without providing associated design input requirements:

1. **"CR & PS Femoral Components"**
2. **"Interlok and Porous Finish on Femoral Components"**
3. **"Cruciate Retaining (CR), CR-Lipped and Posterior Stabilized (PS) Bearings"**

iv. The design inputs documented in Rev. C of the "I0 Risk Table" for DHF #KN152 (completed after the design project and approved on 11/13/2014) are incomplete and/or ambiguous. For example, design inputs such as "Must be able to withstand anticipated loads", "Adequate femoral strength", and those inputs listed to address the user need of "Adequate fixation" are not defined in a manner in which they may be objectively verified. The actual mechanical loads the device must withstand during use have not been defined or documented in the DHF.

D. Procedures for design verification have not been adequately established. For example:

i. During the "TF Mechanical Stability Test (MT2658)" (dated 9/23/2002), your firm determined the maximum force to dislocation for each of the three bearing types (CR, CR Lipped, and PS). While reviewing this design verification study, we observed that:

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a. **Objective acceptance criteria were not defined or shown to have been met during the study. The study concluded that the tibiofemoral stability "is similar to the tibiofemoral stability that has been reported for other total knee systems."**
b. **Justification for the sizes of femoral components and tibial bearings used during the study was not documented to provide objective evidence that the worst-case condition(s) were challenged. Specifically:**

    1. **Size (b) (4) mm femoral components were tested. The smallest and largest sizes within the scope of the design project were (b) (4) mm and (b) (4) mm, respectively.**
    2. **Size (b) (4) mm x (b) (4) mm (thickness) tibial bearings were tested. The smallest and largest sizes within the scope of the design project were (b) (4) mm and (b) (4) mm, respectively. Each size was also offered in thicknesses between (b) (4) mm and (b) (4) mm.**

c. **Valid statistical rationale for the sampling plans used was not documented. 5 or 6 specimens were tested for each of the three bearing types (CR, CR Lipped, and PS).**

ii. **During the "Tibiofemoral Contact Area Test (Mf2656)" (dated 8/22/2002), your firm determined the tibiofemoral contact area for 4 different femoral component/tibial bearing combinations:**

Femoral Component	Tibial Bearing
(b) (4) mm CR	(b) (4) mm x mm CR
(b) (4) mm CR	(b) (4) mm x mm CR
(b) (4) mm CR	(b) (4) mm x mm CR Lipped
(b) (4) mm PS	(b) (4) mm x mm PS

While reviewing this design verification study, we observed that:

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a. **Objective acceptance criteria were not defined or shown to have been met during the study. The study concluded that the contact areas are "similar to the contact area that has been reported for other total knee systems."**
b. **The applied loads used during the study were based on [redacted] The study references literature in which the same assumed body weight was used; however, justification for why this assumed body weight was acceptable for the purposes of this study was not documented.**
c. **Valid statistical rationale for the sampling plans used was not documented. Each femoral component / tibial bearing combination was tested [redacted] times at each of [redacted].**

E. Procedures for design validation have not been adequately established. Specifically:

i. The DHF contains two items which the design and development plan identifies as design validation activities. The documentation does not provide objective evidence that the device conforms to user needs and intended uses. Specifically, the documentation entails:

a. **A one-page letter from a surgeon dated 2/18/2003 that states, in part: "I wanted to advise you that the implantation of the first [device] is going along extremely well." Notably, the letter indicates that the PS version of the device was not assessed at the time, as it states: "I certainly am waiting for the PS components and look forward to you bringing those".**
b. **Literature showing that "Use of a similar device (Maxim) resulted in acceptable performance." Your firm's Development Director, Transformative Technology, Knees explained that Maxim is the most direct predicate device for the Vanguard knee system but described several differences between the Maxim and Vanguard knee systems, including but not limited to (b) (4) [redacted] As such, the literature does not provide evidence that the Vanguard knee system was validated.**

ii. Your firm could not provide objective evidence that all identified design risks were adequately mitigated. *INST 4.0.2.1: Risk Assessment Work Sheet*

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(approved 11/9/2001) identifies "Tolerance stack-up" as a potential risk (hazard). Your firm's Product Development Engineer stated that a tolerance stack-up analysis was not documented.

Between 7/1/2014 and 10/17/2016, your firm distributed (b) (4) devices having part numbers within the scope of DHF #KN152.

Observation 4 Investigation and Response:

Earlier this year, Zimmer Biomet self-identified issues at the Warsaw North Campus concerning the establishment and maintenance of design controls. (b) (4) (b) (4) (b) (4) design controls on behalf of Zimmer Biomet at the Warsaw North Campus and identified numerous issues (see attachment 4-A, *CA-02719* (b) (4)). In response, on July 19, 2016, Zimmer Biomet initiated CAPA CA-02719 (see attachment 4-B, *CAPA CA-02719 Summary*). CAPA CA-02719 is currently in the Investigation (Root Cause/Action Plan) Phase. After the recent inspection, Zimmer Biomet determined that all of the design control issues identified in Observation 4 are within the scope of CAPA CA-02719.

Zimmer Biomet took steps to contain the design control issues identified (b) (4) . (b) (4)

As a result of the recent inspection, Zimmer Biomet determined that additional containment activities are necessary. (b) (4) This will be accomplished (1) by updating an existing work instruction (see attachment 4-D, INST 4.3.1.5, *Design History File Review Checklist*) to include the specific issues identified (b) (4) and (b) (4)

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(b) (4)) review the proposed products' DHF against the DHF checklist (see attachment 4-H, SOP 4.3.1, *Project Initiation & Design History File*). Second, as an additional interim control, Zimmer Biomet will require that new corporate procedures for Design Control and Risk Management, , are used in the development of products at the Warsaw North Campus in lieu of legacy Biomet procedures (i.e., QM 4.3 and QM 4.4). Finally, Zimmer Biomet will evaluate ((b) (4) the containment of DHF #KN152, the DHF cited in Observation 4, which contains components (see attachment 4-C). CAPA CA-02719 was demoted to the correction phase in order to add these additional containment activities.

Pursuant to CAPA CA-02719, Zimmer Biomet conducted an investigation that included the following tasks:

1. Execute the protocol for evaluating the (b) (4) identified (b) (4) one DHF identified by the FDA inspection;
2. Analyze and review the CAPA database to identify open CAPAs related design control;
3. Evaluate containment of any CAPAs found as a result of investigation task #2;
4. Map any CAPAs identified in investigation task #2 to the audit results so that like issues may be addressed together;
5. Conduct a root-cause analysis that addresses all identified design control issues;
6. Identify actions needed to correct and prevent recurrence of the design control problems and establish a verification of effectiveness ("VoE") to ensure that root causes have been corrected; and
7. Review Observation 4 to determine whether all of the design control issues identified in the observation are within the scope of CAPA CA-02719.

The investigation revealed (b) (4)

Zimmer Biomet initiated HHEDs whenever a finding of the investigation suggested (b) (4) . Across the seven product families, Zimmer Biomet initiated (b) (4) HHEDs for this reason. The HHEDs (b) (4) in total) were resolved as follows: (b) (4) have now been closed, (b) (have been elevated to a Health Hazard Evaluation ("HHE"), and (b) (4) remain open (see attachment 4-J *CA-02719 Containment Update*). As a result of these activites, products from (b) (4)

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The determination reached in HHEDs 09-2016-106 and 09-2016-109 pertaining to DHF #KN000223 was that the issues should be excalated to the HHE process, so Zimmer Biomet initiated HHEs 2016-319 and 2016-320. They are still in process, and will be completed by (b) (4). Zimmer Biomet will provide details regarding any decisions reached or actions taken as a result of the HHEs in our update on (b) (4)

In addition, the investigation revealed tha (b) (4)

As part of the investigation, Zimmer Biomet conducted a root-cause analysis under CAPA CA-02719 and determined that design control procedures at the Warsaw North Campus (b) (4)

The root-cause analysis determined that this was because (b) (4)

.

(b) (4)

. (b) (4)

(b) (4) . Zimmer Biomet will evaluate all procedures, forms, and work instructions within this (b) (4) documentation to ensure that the quality system is compliant with the requirements of 21 C.F.R. § 820.30. Specifically, Zimmer Biomet will ensure that the procedures, forms, and work instructions:

1. Include plans that describe or reference design and development activities and define responsibility for implementation, including identifying and describing the interfaces with different groups or activities that provide design inputs;
2. Ensure that formal documented reviews of the design results are planned, conducted, and approved at appropriate stages of the device's design development;
3. Ensure that the design requirements relating to a device (i.e. design inputs) are appropriate and address the intended use of the device, including a mechanism for addressing incomplete, ambiguous, or conflicting requirements;
4. Provide for design verification that requires documentation of the identification of the design, methods of the verification (including objective acceptance criteria, testing of worst-case conditions, and use of sampling plans supported by valid statistical

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rationales), the date of the verification, and the individuals performing the verification; and

5. Procedures for design validation that requires ensuring that devices conform to defined user needs and intended uses, including testing production units under actual or simulated use conditions and conducting a risk analysis where appropriate.

(b) (4)

(b) (4)

Zimmer Biomet will release these new Design Control and Risk Management procedures as an interim control on the Warsaw North Campus. This interim control will continue until the new procedures are fully implemented through the standard company process for the release of a set of corporate procedures, forms, and work instructions.

Upon release of the interim control Design Control and Risk Management procedures on the Warsaw North Campus, Zimmer Biomet will remediate all documentation associated with active DHFs (i.e., DHFs for implants and instrumentation that are still being distributed). (b) (4)

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(b) (4)

Completed Actions:

No.	Action	Completion Date
4-1	Had (b) (4) of design controls at the Warsaw North Campus (see attachment 4-A).	March 18, 2016
4-2	Initiated CAPA CA-02719 (b) (4) (see attachment 4-B).	July 19, 2016
4-3	Analyzed and reviewed the CAPA database to identify open CAPAs related to design control.	September 29, 2016
4-4	Determined that there were (b) (4)	September 29, 2016

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	(b) (4) .	
4-5	Mapped open CAPAs related to design control to the (b) (4) audit results so that like issues could be addressed together (see attachment 4-F).	September 29, 2016
4-6	Executed the protocol for evaluating both nonconformances and complaints to determine whether Warsaw North Campus product lines whose DHFs were audited by (b) (4) were performing as anticipated (see attachment 4-C).	September 30, 2016
4-7	Determined that only one product family had experienced a complaint rate higher than expected, on two separate risk lines, which were addressed with an HHED and a CAPA (see attachment 4-E).	September 30, 2016
4-8	Initiated HHED in connection with the (b) (4) DHFs that were audited by (b) (4).	September 30, 2016
4-9	Conducted a root-cause analysis that addressed all identified design control issues (see attachment 4-G).	December 1, 2016
4-10	Identified actions needed to correct and prevent recurrence of the design control problems.	December 2, 2016
4-11	Established a VoE plan to ensure that root causes have been corrected.	December 2, 2016
4-12	Reviewed Observation 4 to determine whether all of the design control issues identified in the observation are within the scope of CAPA CA-02719.	December 2, 2016
4-13	Updated an existing work instruction (see attachment 4-D) that prevents release of products with DHFs having the same issues identified by (b) (4) and FDA.	December 16, 2016
4-14	Implemented an interim control that prohibits the release of any product using the Warsaw North Campus design control process without evaluation by (b) (4) (see attachment 4-H).	December 16, 2016
4-15	Evaluated the containment of DHF #KN152 (see attachment 4-I).	December 16, 2016
4-16	Closed (b) (4) HHEDs that were generated from the (b) (4) audit results (see attachment 4-J).	December 16, 2016
4-17	(b) (4)	December 16, 2016
4-18	Completed Health Hazard Evaluation HHE 2016-321 for the (b) (4) DHF #KN152 (see attachment 4-M).	December 20, 2016

Planned Actions:

No.	Action	Completion Date
4-19	Complete Root Cause / Action Plan Phase	(b) (4)
4-20	Complete the HHE process pertaining to the products in Design History File (b) (4) . (HHE#: 2016-319, 2016-320)	(b) (4)

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4-21	Evaluate all procedures, forms, and work instructions within the draft Design Control and Risk Management documentation to ensure that the quality system is compliant with the requirements of 21 C.F.R. § 820.30.	(b) (4)
4-22	(b) (4) .e., QM 4.3 and QM 4.4).	(b) (4)
4-23	Assess any HHEDs generated from the containment evaluation of DHF #KN152 to determine if any HHEs or product holds are necessary.	(b) (4)
4-24	(b) (4)) is compliant with the requirements of 21 C.F.R. § 820.30.	(b) (4)
4-25	Remediate all documentation associated with active DHFs (i.e., DHFs for implants and instrumentation that is still being distributed) by reviewing such DHFs against revised procedures, forms, and work instructions so as to conform to those revised procedures, forms, and work instructions.	(b) (4) . More specific date to be reported in a future update
4-26	Complete Action Implementation Phase	Target completion date to be reported in a future update
4-27	Execute the VoE plan by reviewing a sample of active or completed DHFs to determine if DHF documents comply with the revised procedures, forms, and work instructions.	Target completion date to be reported in a future update

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FDA Observation 5

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FDA Observation #5

Procedures for corrective and preventive action have not been adequately established.

Specifically,

A. *CP 1409: Determining Need for HHE* (Rev. 3, effective 3/20/2014) does not adequately establish requirements for analyzing data sources to identify existing or potential quality problems. *CP 1409* states that "Form CF1405 HHE Determination will be initiated to determine if an HHE or field action is required pursuant to CP1406 Field Action Activities." *CP 1406* (Rev. *5,* effective *9/11/2015)* defines a Health Hazard Evaluation (HHE) as an "evaluation of the health hazard presented by a product being considered for recall or other corrective or removal action." While reviewing 17 of the 313 Health Hazard Evaluation Determinations (HHEDs) initiated between 07/01/2014 and 09/12/2016, we observed:

i. HHED forms as well as Section 7.2.5 of *CP1409* ask "Does the product issue or event: 1) Reasonably pose a potential risk to health based on Trend Analysis or previously unidentified risk? If Yes, an HHED Meeting is required." The purpose of HHED Meetings is to determine escalation to HHE. However, according to your firm's Field Action Leader, the way "Trend Analysis" is to be conducted is not defined by procedure. In 17 of 17 HHEDs sampled, this question was answered as "No".

ii. 2 of the 17 HHEDs sampled (HHED #00237 and #00293) relate to complaints of foreign substances found in the sterile packaging of Class II Juggerknot sports medicine devices. The complaint devices associated with HHEDs #00237 and #00293 completed manufacturing on 12/02/2015 and 03/02/2016, respectively. The devices were packaged in the same work center ((b) (4)). During the inspection, we identified 34 *Product Deviation/Reject Reports (i.e.,* nonconforming product recalls) related to debris in packaging that originated from work center (b) (4) between 12/02/2015 and 03/02/2016. This finding was not documented in the investigation notes of either HHED. According to the Field Action Leader, the *Product Deviation/Reject Reports* were not considered in the "Trend Analysis".

In addition to the 17 HHEDs sampled, we observed 2 other HHEDs (#00216 and #00245) initiated due to similar complaints received for Juggerknot sports medicine devices on 1/5/2016 and 1/19/2016. The complaint devices were again packaged in work center (b) (4) and completed manufacturing on 12/08/2015 and 12/28/2015.

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(b) (4) devices from the Juggerknot sports medicine device family were sealed in work center (b) (4) between 12/02/2015 and 03/02/2016, of which 12,110 devices have been distributed. 4 complaints related to debris in sterile packaging were reported from these 12,110 devices. All 4 resulted in HHEDs (00216, 00237, 00245 and 00293). None of the 4 HHEDs were escalated to an HHE.

Observation 5A Investigation and Response:

On December 1, 2016, Zimmer Biomet opened CAPA CA-03078 to investigate and address the findings in Observation 5(A) regarding deficiencies in the Health Hazard Evaluation Determination ("HHED") process at the Warsaw North Campus (see attachment 5A-A, *CA-03078 CAPA Summary*). CA-03078 is currently in the Correction Phase.

Zimmer Biomet's preliminary investigation of the issues identified in Observation 5(A) determined that the (b) (4) The previous HHED procedure and form, under which the four HHEDs identified in sub-part (ii) of Observation 5(A) were processed, have been obsoleted; they were superseded by procedure CP04100, *Health Hazard Evaluation (HHE) Process*, Rev. 1 and the associated HHED form, CF04100, *Health Hazard Evaluation Determination Form*, Rev. 1 (see attachments 5A-B, *CP04100, Rev. 1*, and 5A-C, *CF04100, Rev. 1*). Both CP04100 and CF04100 were implemented at the Warsaw North Campus during in the recent FDA inspection, on September 22, 2016, with a requirement that all in-process HHEDs at the time of release of the procedure and form were to be aligned with the new process by November 2, 2016. Zimmer Biomet trained appropriate personnel to the new procedure and form prior to implementation (see attachment 5A-D, *Training Records*).

As a correction, Zimmer Biomet will apply the new HHED form, CF04100, to the four HHEDs referenced in Observation 5(A)(ii), HHEDs #00237, #00293, #00216, and #00245. Each will then be reassessed for the need to escalate to an HHE under the new HHED process. (b) (4)

Zimmer Biomet will also conduct a (b) (4) review and (b) (4) of HHEDs performed prior to the September 22, 2016 implementation of the new HHED form and process. The (b) (4) review will include all HHEDs at the Warsaw North Campus that meet both of

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following criteria: (1) initiated after the last revision to the previous HHED procedure (March 20, 2014) and before the release of the new HHED process (September 22, 2016) and (2) not previously escalated to an HHE.

In addition, Zimmer Biomet will review the newly implemented HHED procedure and form, CP04100 and CF04100, to ensure that it adequately addresses the findings in Observation 5(A). This will include the definition and direction regarding the conduct of trend analysis, as identified in Observation 5(A)(i), and the consideration of non-conforming product reports ("NCRs") and other related HHEDs as inputs to the HHED process, as identified in Observation 5(A)(ii). Further, Zimmer Biomet will audit all HHEDs completed with the newly implemented HHED procedure and form to assess the effectiveness of CP04100 and CF04100 and determine if there are any gaps in the process. Zimmer Biomet will provide details of additional corrective actions taken as result of this analysis in future update responses.

Completed Actions:

No.	Action	Completion Date
5A-1	Implemented new HHE procedure, CP04100, Rev. 1, at Warsaw North Campus (see attachment 5A-B).	September 22, 2016
5A-2	Implemented new HHED form, CF04100, Rev. 1, at Warsaw North Campus (see attachment 5A-C).	September 22, 2016
5A-3	Initiated CAPA CA-03078 to address the issues identified in Observation 5(A) (see attachment 5A-A).	December 1, 2016
5A-4	Trained personnel to new CP04100 and CF04100 (see attachment 5A-D).	December 12, 2016
5A-5	Identified (i) all HHEDs within scope for (b) (4) review and (b) (4) and (ii) all HHEDs completed with the newly implemented HHED procedure and form (see attachment 5A-E, *List of HHEDs*).	December 13, 2016

Planned Actions:

No.	Action	Completion Date
5A-6	Apply CF04100, Rev. 1 to HHEDs #00237, #00293, #00216, and #00245, and reassess HHED decision per CP04100.	(b) (4)
5A-7	Assess effectiveness of CP04100 and CF04100 against the findings of Observation 5(A)(i) and 5(A)(ii) and audit all HHEDs completed prior to the opening of this CAPA (December 1, 2016) with the newly implemented HHED procedure and form to identify any gaps in the new procedure and form.	(b) (4)

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5A-8	Complete CA-03078 Root Cause/Action Plan Phase	(b) (4)
5A-9	Complete (b) (4) review and (b) (4) of HHEDs identified in Action 5A-5(i), transfer the HHEDs to revised HHED Form CF04100, evaluate the HHED decision per revised CP04100, and address any gaps identified in Action 5A-7.	Target completion date to be reported in a future update
5A-10	Complete CA-03078 Implementation Phase.	Target completion date to be reported in a future update
5A-11	Verify effectiveness of CA-03078 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #5B

B. Corrective actions have not been effective in preventing recurrence of quality problems. Specifically, Corporate CAPA #CA-02208 was initiated on 11/17/2015 after "it was found the Preventive Action process was used when there is a clear nonconformity" and "Initial investigations found this issue is recurring at other Zimmer Biomet sites." As a "Containment and/or Initial Correction" action, the CAPA references a memo sent to all Zimmer Biomet facilities on 9/25/2015, which states, in part:

(b) (4)

Each of the 2 preventive actions your firm has initiated since the memo was disseminated has been incorrectly categorized as a preventive action rather than a corrective action. Specifically:

i. Preventive action #PA-00538 was initiated on 1/7/2016. As of 9/14/2016, the problem statement read: "The scope of the PA is to compare the development of multiple (b) (4) **sterilization product families and the supporting activities." During our review of your firm's** (b) (4) **sterilization product families, we observed the existing nonconformances described in Observation l(A).**

ii. Preventive action #PA-00539 was initiated on 1/7/2016. As of 9/13/2016, the problem statement read: (b) (4)

"

During our review of the "Lactosorb" (b) (4) **cycle (**(b) (4) **validation, we observed the existing nonconformances described in Observation 1(B).**

Observation 5B Investigation and Response:

On December 6, 2016, Zimmer Biomet opened CAPA CA-03103 to investigate and address the findings identified in Observation 5(B) regarding the use of Preventive Actions at the Warsaw

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North Campus when Corrective Actions should be used (see attachment 5B-A, *CA-03103 CAPA Summary*). CA-03103 is in the Investigation/Action Plan Phase.

Prior to the inspection, Zimmer Biomet replaced the Corporate CAPA procedure, CP1400 Rev. 6, *Corrective and Preventive Action*, with CP07000, Rev. 1, *Corrective and Preventive Action* (see attachment 5B-B, CP07000 Rev. 1). The new procedure includes instructions for when to identify an issue and its related CAPA as a Corrective Action or a Preventive Action. This corporate procedure was released and made available on May 2, 2016 to add the following section:

(b) (4)

Further, on May 2, 2016, Zimmer Biomet configured the software used for the facility's CAPA system, (b) (4), to require that both Preventive Actions and Corrective Actions would be processed using the same form and workflow. (b) (4)

As an immediate correction, Zimmer Biomet transferred the content of both Preventive Actions identified in Observation 5(B), PA-00538 and PA-00539 (see attachments 5B-C PA-00538 and 5B-D PA-00539, to new Corrective Action files, CAPAs CA-02978 and CA-02867, respectively (see Attachments 5B-E CAPA CA-02978 and 5B-F CAPA CA-02867). Zimmer Biomet closed PA-00538 and PA-00539. In addition, Zimmer Biomet will investigate under CAPA CA-03103 why PA-00538 and PA-00539 were opened as Preventive Actions rather than Corrective Actions, despite the issuance of a Corporate memorandum regarding the proper use of Corrective and Preventive Actions. Following the completion of the investigation, Zimmer Biomet will provide in future updates to this response information regarding corrective actions, if any, determined to be necessary to reinforce the proper use of Corrective and Preventive Actions. In the investigation conducted under CAPA CA-03103, Zimmer Biomet will also seek to determine why the communication regarding the distinction between Corrective and Preventive Actions issued under Corporate CAPA CA-00208, as identified in Observation 5(B), was not correctly implemented at the Warsaw North Campus. Zimmer Biomet will provide information regarding any related corrective actions determined to be appropriate in future updates to this response.

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Zimmer Biomet's (b) (4) team will conduct a review of all open Preventive Action records (b) (4) total as of December 2, 2016) at the Warsaw North Campus to determine whether the problem statement for each action references an actual or potential non-conformance. For any open Preventive Actions that are found to reference an actual non-performance, the files were converted to Corrective Actions. The (b) (4) team will also conduct a (b) (4) review of Preventive Action records from the Warsaw North Campus that are now closed but were opened in the preceding (b) (4) The review will assess each closed Preventive Action record to determine if the issue addressed by the Action still exists, and if so, if remediation of the record is required. Zimmer Biomet will also assess the open and closed Preventive Action records that are converted to Corrective Actions to determine whether product containment actions are required. Zimmer Biomet will provide information regarding such containment actions, if any are required, in future updates to this response.

Completed Actions:

No.	Action	Completion Date
5B-1	Revised section 7.4.2 of CP07000 Rev. 1, to provide direction regarding the appropriate use of Corrective Actions and Preventive Actions (see attachment 5B-B CP07000 Rev. 1).	May 2, 2016
5B-2	Initiated CAPA CA-03103 to address the issues identified in Observation 5(B) (see attachment 5B-A).	December 6, 2016
5B-3	Transferred Preventive Action PA-00538 content to Corrective Action CAPA CA-02978 and voided PA-00538 (see attachment 5B-C PA-00538). The PA and CA records are linked together in (b) (4) .	December 20, 2016
5B-4	The actions for Preventive Action PA-00539 are complete and the record will be closed. PA-00539 is linked to Corrective Action CAPA CA-02867 which will address the nonconformities in Observation 1B (see attachment 5B-D PA-00539).	December 20, 2016

Planned Actions:

No.	Action	Completion Date
5B-5	Review incorrect PA records to provide information for the root cause analysis.	(b) (4)
5B-6	Review open Preventive Actions at the Warsaw North Campus to determine whether any actions concerning non-conformities were incorrectly created as Preventive, rather than Corrective Actions.	(b) (4)
5B-7	Review closed Preventive Actions that were opened in the last two years at the Warsaw North Campus to determine whether	(b) (4)

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	remediation activities are required.	
5B-8	Complete CAPA CA-03103 Root Cause / Action Plan Phase.	(b) (4)
5B-9	Complete CAPA CA-03103 Implementation Phase.	Target completion date to be reported in a future update
5B-10	Complete CAPA CA-03103 Verification and Final Closure Phase.	Target completion date to be reported in a future update

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FDA Observation #5(C)

C. Procedures for investigating the cause of nonconformities have not been adequately established. Specifically, CAPA #CA-01770 was initiated on 10/28/2014 due to an adverse "deviation" *(i.e.,* nonconforming product) trend identified in ultra-high-molecular-weight polyethylene (UHMWPE) (b) (4) bar stock. Your firm's Associate Director of Biomaterials Research explained that the cause of the trend was "faint white lines" visually identified in the bar stock. As part of the CAPA, your firm subjected (b) (4) bar stock exhibiting faint white lines to density and crystallinity testing and determined that "no significant difference exists between the faint white lines and the rest of the (b) (4) barstock." However, in addition to density and crystallinity, *QP0001: Manufactured Poly Bar* (b) (4) *) Testing Requirements* (Rev. 10, effective 12/18/2014 to 10/21/2016) requires (b) (4) bar stock to [be] tested for tensile strength per method *Q00838*. Tensile testing was not performed within CAPA #CA-01770 to demonstrate that (b) (4) bar stock exhibiting faint white lines meets tensile strength requirements, which are based on the *ASTM F648* standard for UHMWPE surgical implants. Despite this, the CAPA concludes that "since the analysis of the faint white lines deemed them acceptable, no more deviations will be written for faint white lines." As of 9/28/2016, a conclusive root cause of the faint white lines has not been determined.

Between 7/1/2014 and 10/13/2016, your firm distributed (b) (4) lots (total of (b) (4) devices) manufactured out of (b) (4) bar stock. In addition, between 7/1/2014 and 9/9/2016, your firm distributed (b) (4) inches of (b) (4) bar stock to other Zimmer Biomet facilities for their manufacturing of finished devices.

Observation 5(C) Investigation and Response:

On October 28, 2014, Biomet initiated CAPA CA-1770 to address a nonconforming product trend—i.e., the presence of "faint white lines"—on ultra high molecular weight polyethylene (b) (4)) bar stock manufactured at the Warsaw North Campus. Faint white lines were not defined in the inspection method (Q00478) as a basis for rejection, but CAPA CA-1770 nevertheless was initiated. (b) (4)

(b) (4)

. Biomet updated inspection method Q00478 (b) (4)

. Biomet closed CAPA CA-1770 on March 2, 2015.

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During the recent inspection, FDA inspectors observed that, although required for process monitoring, no (b) (4) testing was conducted under CAPA CA-01770 to directly investigate the (b) (4) of (b) (4) bar with faint white lines. In addition, the report of the testing conducted at the time did not include a justification for the exclusion of (b) (4) testing.

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03079 to address the issues identified in Observation 5(C) (see attachment 5C-A, *CAPA CA-03079)*. CAPA CA-03079 currently is in the Investigation (Root Cause/Action Plan) Phase.

As part of the (b) (4) validation (b) (4) testing was completed on both (b) (4)

As reasonable proxies for (b) (4) testing, (b) (4) tests were chosen as part of the CAPA CA-01770 investigation for their test specimen geometries. (b) (4)

.

After CAPA CA-01770 was discussed during the FDA inspection, Zimmer Biomet completed a protocol for (b) (4) testing (see Attachment 5C-B, (b) (4) bar stock in production orders was subjected to (b) (4) testing to identify bars with faint white lines. Zimmer Biomet subsequently conducted additional testing of bars that included faint white line indications to determine if the (b) (4) of those bars met specifications in support of the findings of CAPA CA-01770. (b) (4)

). As such, the results of the (b) (4) testing (b) (4)

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(b) (4)

Due to the passing (b) (4) test results and the data collected in CAPA CA-01770, Zimmer Biomet determined (b) (4) Similarly, Zimmer Biomet determined (b) (4) (b) (4) (b) (4)). With respect to finished devices manufactured using bar stock with faint white lines that have been distributed, Zimmer Biomet completed a health hazard evaluation–determination ("HHED") (see attachment 5C-E, *HHED 09-2016-070*) that concluded that a (b) (4)

Pursuant to CAPA CA-03079, Zimmer Biomet will:

1. Conduct a root-cause analysis of the issues identified in Observation 5(C) concerning the failure of the CAPA investigation to perform required (b) (4) testing;
2. Develop a CAPA CA-03079 Implementation Plan; and
3. Develop a verification of effectiveness ("VoE") plan for CAPA CA-03079.

Completed Actions:

No.	Action	Completion Date
5C-1	Initiated CAPA CA-03079 to address the issues identified in Observation 5(C) (see attachment 5C-A, *CAPA CA-03079 Summary*).	December 1, 2016
5C-2	(b) (4)).	October 7, 2016
5C-3	(b) (4) bar stock in production orders to identify bars with faint white lines.	October 7, 2016
5C-4	Subjected bar stock with faint white lines to (b) (4) testing and established with (b) (4) that the mean of the (b) (4) would meet the acceptance criteria at all depths (see attachment 5C-C, Report, (b) (4) *).*	October 28, 2016
5C-5	Initiated CAPA CA-03079 to address issue associated with not completing (b) (4) testing as part of CAPA CA-01770 (see attachment 5C-A, *CAPA CA-03079 summary).*	December 1, 2016
5C-6	Completed an HHED (see attachment 5C-E, *HHED 09-2016-070*) (b) (4) .	December 9, 2016

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Planned Actions:

No.	Action	Completion Date
5C-7	Conduct a root-cause analysis of the issues identified in Observation 5(C) concerning the failure of the CAPA investigation to perform required testing.	(b) (4)
5C-8	Complete CAPA CA-03079 Investigation (Root Cause/Action Plan) Phase	(b) (4)
5C-9	Complete CAPA CA-03079 Implementation Phase.	Target completion date to be reported in a future update
5C-10	Verify effectiveness of CAPA CA-03079 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation 6

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FDA Observation #6(A)

Process control procedures that describe any process controls necessary to ensure conformance to specifications have not been adequately established.

Specifically,

A. Your firm's procedures for packaging sterile/non sterile devices do not ensure that packaging operations are adequately controlled or that package sealing operations for terminally sterilized devices will meet specified requirements. For example:

i. Package sealer parameters are not documented in PES 1.31 Rev. 91 in a manner that prevents misuse. For example, for tray/blister sealing machine (b) (4) 12 out of 17 different parameter groups have documented numerical minimum settings, but maximum settings of "N/A." In conversations with firm management they stated this indicates a validated single set point instead of a range. There are no statements in the procedure to clarify that the appearance of specified minimum settings with "N/A" maximum settings means that only the minimum settings can be used. Review of sealing parameter logs for sealer (b) (4)) spanning the time frame from 06/29/2016 to 10/10/2016 revealed that one (1) lot was sealed using parameters that were higher than the minimum settings specified for single set point parameter groups. This lot (M584030, item 905945P, All-Thread PEEK-Optima Soft Tissue Fixation devices) consisting of (b) (4) units was not found as nonconforming at the time of sealing.

ii. Package sealer parameters are not consistently documented in the Process Engineering Specification 1.31 to ensure that operators are using validated process parameters. For example:

a. From 01/01/2006 to 07/31/2006, your firm manufactured (b) (4) production lots of Mimix microfixation devices on Sealer (b) (4) using die (b) (4) with parameters that were not validated for use when the equipment was moved from (b) (4) to (b) (4) (b) (4) of these lots consisting of (b) (4) devices were distributed to customers. After the sealer/die were installed in (b) (4) , your firm's OQ performed in November of 2005 tested seal pressure ranges from (b) (4) (b) (4) psi for optimal temperature and dwell settings of (b) (4) °F and (b) (4)

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seconds respectively. The validation concluded that nominal settings for the machine were (b) (4)°F, (b) (4) seconds, and (b) (4) psi, but these settings were never transferred to PES 1.31. When the (b) (4) production lots of Mimix devices were manufactured, the only document containing specifications for this sealer/die combination was Process Specification (PS) 9.50 Rev. 26, effective 05/03/2005. PS 9.5 documented settings of (b) (4)°F, (b) (4) seconds, and (b) (4) psi. These settings were not revalidated after the sealer was moved to (b) (4)

b. Process Engineering Specification 1.31, Rev. 91 effective 09/20/2016, incorrectly references parameters and/or provides parameters outside of the validation ranges the following dies on sealer (b) (4) For example:

1. **Seven (7) out of nine (9) dies listed in 1.31 incorrectly identified the maximum and/or minimum parameters for air pressure. Six (6) of seven (7) of the dies had a maximum and minimum air pressure identified as "N/A" when the corresponding validations for those dies utilized (b) (4) psi. One (1) out of seven (7) of the dies provided a minimum air pressure of (b) (4) psi, but a maximum air pressure of N/A when both should be (b) (4) psi.**

2. **Two (2) out of nine (9) dies listed in 1.31 incorrectly identify the maximum validated range for dwell time as (b) (4) when the corresponding validations for those dies used (b) (4) seconds.**

Observation 6(A) Investigation and Response:

Prior to the recent FDA inspection, on March 8, 2016, Zimmer Biomet initiated CAPA CA-02380 to address (b) (4) (see attachment 6A-A, *CAPA CA-02380 Summary*). The issues included: (b) (4) In response to the FDA inspection, the findings contained in Observation 6(A) were added to CAPA CA-02380, including single, minimum, or set points listed as not applicable ("N/A") for all sealing process parameters. This applies to procedures for process control of

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packaging operations that do not ensure that (i) packaging operations are adequately controlled or that (ii) package sealing operations for (b) (4) sterilized devices will meet specified requirements. CAPA CA-02380 is in the Investigation (Root Cause/Action Plan) Phase.

During the recent FDA inspection of the Warsaw North Campus, the FDA investigators identified that some sealers in the sterile packaging cleanrooms were being operated outside of their validated ranges. As a result of this observation, (b) (4) . Zimmer Biomet assessed all active sealing and die reports to determine whether there was appropriate technical data to support releasing sealers back to production or whether individual sealers should remain out of production. All sealers were evaluated per existing SOP 9.4.17 and documented using INST 9.4.17.1 (see attachment 6A-B, *SOP 9.4.17* (b) (4) (b) (4) *and INST 9.4.17.1* (b) (4)) to determine if:

- Process Specification production parameters documented within the appropriate Process Engineering Specification ("PES"), Packaging Sterile/Non-sterile were within the validated operational qualification ("OQ") and performance qualification ("PQ") limits, as required by Question 1 of instruction INST 9.4.17.1;

- OQ testing challenged the range of operational control limits, as per Question 2 of INST 9.4.17.1; and

- The reports were acceptable to satisfy the requirements listed in the protocol of Question 5 of INST 9.4.17.1.

Zimmer Biomet identified (b) (4) (b) (4) .
Zimmer Biomet's review identified (b) (4) (b) (4) (b) (4) –(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)).

- (b) (4) .

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- This protocol was later transferred to Interim Control IC 021, (see attachment 6A-E, *IC-021,* (b) (4) (b) (4) *, Rev. 1*), on November 11, 2016. Under the process monitoring protocol and IC 021, operators document sealer parameter settings on sealing parameter logs, Manufacturing Process Form MPF #0088, (b) (4) (b) (4) (b) (4) . These documentation steps function as process containment to verify that sealing process parameters are being used appropriately.

- (b) (4)
  (b) (4)
  .
- (b) (4)
- (b) (4)
  - (b) (4)

(b) (4)
(D) (4).

- (b) (4)
  .
- (b) (4)
  (b) (4)
).

With respect to Observation 6(A)(ii)(a) regarding the use of component (b) (4) with sealer (b) (4) without revalidation after moving the equipment from (b) (4) to (b) (4) at the Warsaw North Campus, there are no lot- or equipment-specific containment actions that Zimmer Biomet can take at this time. The (b) (4) production lots of (b) (4) manufactured using sealer (b) (4) and component (b) (4) have a (b) (4) shelf life and would have expired (b) (4); thus, they cannot be included on a quality hold or assessed for field action. Further, the die that was used for sealing components (b) (4) was transferred to a Zimmer Biomet facility (b) (4), and therefore no validation was performed in 2006 for this sealing die following the validation activities conducted at Warsaw North Campus (b) (4) in 2005.

In addition, Zimmer Biomet has also implemented corrections to address the findings in the Observation 6(A)(i). As observed by the FDA Investigators in Observation 6(A)(i), the documentation for sealer (b) (4) contained documented numerical minimum settings but maximum settings of "N/A" for (b) (4) out of (b) (4) parameter groups for the sealer. "N/A" was used for maximum settings when there was a single set point for the parameter, identified as the minimum setting. The (b) (4) parameter groups for sealer (b) (4) that had "N/A" as a maximum setting utilize a total of (b) (4) sealing dies. As an immediate correction in response to Observation 6(A)(i), Zimmer Biomet provided appropriate maximum sealing parameters settings for the (b) (4) dies associated with the (b) (4) groups of parameters for sealer (b) (4) that previously lacked numerical maximum settings. Zimmer Biomet completed all updates to "PES" 1.31, Rev. 91 resulting from Observation 6(A), on December 15, 2016 when PES 1.31, revision 97 became effective (See

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attachment 6A-N, (b) (4) *1.31, Rev. 97*). Operators will be trained to the revisions in PES 1.31 Rev. 97, within 30 days of Rev. 97's effective date.

As an containment action to address the finding in Observation 6(A)(i), Zimmer Biomet placed item number (b) (4) (All-Thread PEEK-Optima Soft Tissue Fixation devices) with lot number M584030 (which was identified in the Observation as non-conforming at the time of sealing due to the documentation of an out of specification parameter) on (b) (4) . In addition, during the inspection, Zimmer Biomet implemented increased monitoring of the package sealing process. On November 4, 2016, Zimmer Biomet transferred a recently imposed requirement that packaging operators document actual parameter settings when using sterile sealers (implemented prior to the inspection under (b) (4) to an Interim Control document IC 019, (see attachment 6A-P, *IC-019,* (b) (4) *Rev. 1*). Under IC-019, operators document actual sealer parameter settings on sealing parameter logs MPF-0088 (see attachment 6A-Q, *Manufacturing Process Form MPF-0088*), which were already in use prior to the inspection. This increased monitoring has allowed for the early detection of packaging process issues and demonstrates that sterile packaging sealing processes are creating packages that conform to specifications, while improved process controls are created and implemented during the remediation process.

In addition, as identified in Observation 6(A)(ii)(b)(1), (b) (4) dies utilized on sealer (b) (4) had (b) (4) settings identified as "N/A" in PES 1.31, Rev. 91. In response to the inspection, Zimmer Biomet transferred the air pressure settings from previous validations and recorded them to correct the (b) (4) settings of (b) (4) dies stated in PES 1.31 Rev. 93 (see attachment 6A-R, *PES 1.31,* (b) (4) (b) (4) *, Rev. 93*) on October 19, 2016 to include the appropriate maximum parameter settings. The remaining (b) (4) dies had incorrect maximum settings for (b) (4) as well as (b) (4) documented in PES 1.31, as identified in Observation 6(A)(ii)(b)(2). The correct validated maximum (b) (4) of (b) (4) seconds for dies (b) (4) was incorrectly changed to (b) (4) seconds when PES 1.31 was updated from (b) (4) Zimmer Biomet has determined (b) (4) was utilized by Zimmer Biomet to correct the documentation for the (b) (4) dies specified in Observation 6(A)(ii)(b)(2) that had both incorrect maximum (b) (4) and "N/A" for maximum and minimum (b) (4) (i.e., (b) (4)) to the validated maximum of (b) (4)

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seconds for (b) (4) and added the appropriate pressure settings for the most current revision of PES 1.31, Rev. 97.

Further, Zimmer Biomet took several (b) (4) have been reviewed and approved by Quality (including references to the applicable documentation detailing an investigation, such as NCR, or CAPA) (b) (4)

- (b) (4), referenced earlier in this response, was first implemented (b) (4) and applies to packages produced with documented sealer parameters that are outside the validation parameters ((b) (4) (b) (4)) was completed and no HHE was required.
- (b) (4) as discussed in the cover letter to this response, was first implemented
- (b) (4) as discussed in the cover letter to this response, was first implemented (b) (4) , and (b) (4) .
- (b) (4) was first implemented (b) (4)
- (b) (4) was first implemented (b) (4) (b) (4) between (b) (4)

(b) (4)) and (b) (4) which is still in progress.

Finally, to investigate the need to conduct field actions with respect to distributed product in the field (i.e., (b) (4)), Zimmer Biomet initiated two Health Hazard Evaluation Determinations ("HHEDs"):

- HHED 09-2016-081 (see attachment 6A-T, *HHED 09-2016-081*) was completed and (b) (4) .
- HHED 11-2016-027 (see attachment 6A-AA, *HHED 11-2016-027*) was completed December 13, 2016 (b) (4) .

Under CA-02380, Zimmer Biomet will continue to investigate the issues identified in Observation 6(A). Specifically, Zimmer Biomet will investigate sealer and packaging validations and the change control process to better understand why sealer processes had (b) (4) set points defined for minimum pressure. The investigation will also assess current controls to detect failures. This will include routine sampling, how sampling is established, and investigation processes for any identified failures.

After the completion of this investigation, Zimmer Biomet will identify appropriate corrective actions to address the findings in Observation 6(A) and any other gaps identified through the investigation process. Zimmer Biomet will provide details of timelines for any such corrective actions in future updates to this response.

In addition, our current process monitoring procedure Interim Control, *IC 019* (b) (4) *I*, Rev. 3, includes statistical process monitoring, (b) (4)

Completed Actions:

No.	Action	Completion Date
6A -1	Implemented (b) (4)	September 28, 2016

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6A -2	(b) (4)	September 29, 2016,
6A-3	(b) (4)	September 29, 2016.
6A-4	(b) (4)	October 12, 2016
6A-5	(b) (4)	October 12, 2016
6A-6	(b) (4) (b) (4)	October 12, 2016
6A-7	(b) (4) dies utilized on sealer (b) (4) had air pressure settings identified as N/A in PES 1.31, Rev. 91. In response to the inspection, replaced the N/A pressure setting in the PES 1.31 specification with active validations values. The data transferred and properly recorded the correct (b) (4) settings from the validations into PES 1.31, Rev. 93 for (b) (4) out of the (b) (4) dies(see attachment 6A-R).	October 20, 2016
6A-8	(b) (4)	October 20, 2016
6A-9	(b) (4) (b) (4) between (b) (4) (see attachment 6A-Y).	October 21, 2016
6A-10	Established an increased process monitoring protocol for lot-by-lot testing to release sealer (b) (4) for production on the increased monitoring protocol (see attachment 6A-D).	October 26, 2016
6A-11	Revalidated sealer (b) (4) under IC-014, (see attachment 6A-F).	November 1, 2016
6A-12	Sealing parameter logs MPF-0088, (see attachment 6A-Q)	November 4, 2016
6A-13	Implemented Interim Control IC-019, (b) (4) to increase process monitoring of packaging operations (6A-P).	November 4, 2016
6A-14	Completed challenge testing (b) (4)	November 9, 2016
6A-15	Documented and corrected incorrect maximum settings for dwell	November 10, 2016,

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	time and (b) (4) for (b) (4) dies on Sealer (b) (4) in PES 1.31, Rev. 94 (see attachment 6A-S).	
6A-16	Updated the parameters for sealer (b) (4) to add packaging components and single set points for time, temperature, and pressure (see attachment 6A-I).	November 11, 2016
6A-17	Implemented Interim Control IC-021, (b) (4) to increase process monitoring of packaging operations and require documentation of actual sealer parameter settings (see attachment 6A-E).	November 11, 2016
6A-18	(b) (4)	November 12, 2016
6A-19	(b) (4)	November 28, 2016
6A-20	Completed HHED 11-2016-027. (see attachment 6A-AA).	December 13,2016
6A-21	Completed HHE 2016-301 (see attachment 6A-Z)	December 20, 2016
6A-22	(b) (4) (b) (4) (see attachment 6A-K, attachment 6A-L, and attachment 6A-M)	December 13, 2016
6A-23	Added the Observation 6(A) findings to existing CAPA CA-02830 to address the issues identified in Observation 6(A) regarding process control of packaging operations, including package sealing operations for (b) (4) sterilized devices (see attachment 6A).	December 14, 2016
6A-24	Modified (b) (4) to reflect study/test results from Observation 6(A) (see attachment 6A-N).	December 15, 2016
6A-25	Initiated HHED 09-2016-081 on December 6, 2016, (b) (4) .	December 16, 2016
6A-26	HHED 12-2016-056 was initiated (b) (4)).	December 17, 2016

Planned Actions:

No.	Action	Completion Date

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6A-27	Train operators to Revision 97 of PES 1.31 with respect to package sealer parameters.	(b) (4)
6A-28	Investigate sealer/packaging validation and change control process to better understand why sealer processes had single set points defined for minimum sealing process parameters, and why process specifications were not supported by the validated process parameters	(b) (4)
6A-29	Conduct root cause analysis for CA-02380.	(b) (4)
6A-30	Complete Root Cause/Action Plan Phase	Target completion date to be reported in a future update
6A-31	Complete CA-02380 Action Implementation Phase.	Target completion date to be reported in a future update
6A-32	Verify effectiveness of CA-02380 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #6(B)(i)

B. Procedures to control cleaning processes have not been adequately established. Specifically:

i. On 9/30/2016, we interviewed an operator in Work Center (b) (4), which is a room in the (b) (4) located between (b) (4) During the interview, we observed:

a. We observed a bottle of (b) (4) in Work Center (b) (4), which the operator explained he uses to remove any debris seen on (b) (4) femoral implants. Use of the (b) (4) is not discussed in *WIG0160*. The operator explained that he works in Work Center (b) (4) "every day" and uses (b) (4) to remove debris on "a couple lots a week." He confirmed that such instances are not documented as nonconforming product by means of a *Product Deviation/Reject Report*.

b. We also observed a bottle of (b) (4) cleaning chemical in Work Center (b) (4). Use of (b) (4) is not discussed in *WIG0160.* The operator explained that he always uses (b) (4) instead of (b) (4) but was unsure if any other operators who work in Work Center (b) (4) use the latter.

c. The operator explained that he uses the (b) (4) located in (b) (4) to further clean all femoral devices featuring (b) (4) per *Process Engineering Specification (PES) 1.15* (Rev. 68, effective 5/10/2016). However, while *PES 1.15* states that (b) (4), it does not described at what point in the manufacturing process such components must be (b) (4). Use of the (b) (4) is also not discussed in *WIG0160.* The operator explained that he (b) (4) the implants "until he doesn't see any debris" coming off.

d. *Process Engineering Specification (PES) 1.15* (Rev. 68, effective 5/10/2016) requires (b) (4) to operate at pressure settings between (b) (4) and (b) (4) psi. On 9/30/2016, we observed the (b) (4)

(b) (4) operating at a pressure of (b) (4) psi. Notably, the operator stated that he does not typically check the pressure setting of the (b) (4) prior to use. The pressure gage is located in another room outside of Work Center (b) (4).

Between 7/1/2014 and 10/13/2016, your firm distributed at least (b) (4) devices that were process through 11803/25050.

Observation 6(B)(i) Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03080 to address the issues identified in Observation 6(B)(i)(a)-(b), which concern the presence of unapproved manufacturing material in Work Center (b) (4), where femoral knee implants are cleaned. CAPA CA-03080 currently is in the Investigation (Root Cause/Action Plan) Phase. Zimmer Biomet earlier initiated CAPA CA-02953 on October 12, 2016, and CAPA CA-02645 on June 24, 2016, to address the issues identified in Observation 6(B) (i)(c)-(d) (see attachment 6Bi-A, *CAPA CA-02953 Summary*, and attachment 6Bi-B, *CAPA CA-02645 Summary*). CAPA CA-02953 and CAPA CA-02645 were opened to address concerns about the failure to report nonconforming product and the use of (b) (4) equipment in Work Center (b) (4). CAPAs CA-02953 and CAPA CA-02645 are currently in the Investigation (Root Cause/Action Plan) Phase.

To contain femoral knee implants cleaned under these conditions, Zimmer Biomet initiated (b) (4) on (b) (4) and (b) (4) on (b) (4)). (b) (4) . As an additional containment measure, Zimmer Biomet (b) (4) at the Warsaw North Campus upon the issuance of (b) (4) on (b) (4) until the implementation of Interim Control IC-004 on October 20, 2016 (see attachment 6Bi-E, *IC-004* (b) (4) *, rev 1*). IC-004 describes the necessary process monitoring requirements of (b) (4) (b) (4)), to ensure that product cleanliness is maintained to predetermined Zimmer Biomet requirements, until cleaning processes can be revalidated. This process applies to Warsaw North Campus final clean processes that were validated prior to the initiation IC-004. Zimmer Biomet also implemented Interim Control IC-010 on October 26, 2016, to address concerns about the use of (b) (4) equipment in the work center (see attachment 6Bi-G, *IC-010*). (b) (4) , (b) (4)).

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Pursuant to CAPA CA-03080, CAPA CA-02953, and CAPA CA-02645, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 6(B)(i) related to unapproved use of chemicals ((b) (4) and equipment (a (b) (4)) in the femoral knee implant cleaning process;
2. Review applicable work instructions (WIG0160 and WIG00037) to identify any gaps;
3. Review cleaning operations at the Warsaw North Campus to determine whether unapproved chemicals are being used in those processes;
4. Develop implementation plans for CAPA CA-03080, CAPA CA-02953, and CAPA CA-02645; and
5. Develop verification of effectiveness ("VoE") plans for CAPA CA-03080, CAPA CA-02953, and CAPA CA-02645.

With respect to the at least (b) (4) devices that were cleaned via the (b) (4) cleaning process for femoral knee implants and then distributed between July 1, 2014, and October 13, 2016, Zimmer Biomet initiated a health hazard evaluation determination ("HHED") on October 21, 2016 (see attachment 6Bi-I, *HHED 10-2016-038*). The results of the HHED, and any resulting health hazard evaluation ("HHE") will be provided in a future update to this response.

Completed Actions:

No.	Action	Completion Date
6Bi-1	Initiated CAPA CA-02645 to address the issues identified in Observation 6(B)(i)(c)-(d) (see attachment 6Bi-B).	June 24, 2016
6Bi-2	(b) (4)).	September 29, 2016
6Bi-3	(b) (4)	September 29, 2016
6Bi-4	(b) (4)	October 12, 2016
6Bi-5	Initiated CAPA CA-02953 to address the issues identified in Observation 6(B) (i)(c)-(d) (see attachment 6Bi-A).	October 12, 2016
6Bi-6	Subjected(b) (4) (b) (4)	October 29, 2016
6Bi-7	Implemented IC-004 which establishes process monitoring requirements to ensure that product cleanliness is maintained to predetermined Zimmer Biomet requirements until cleaning processes can be revalidated (see attachment 6Bi-E).	October 20, 2016
6Bi-8	Initiated an HHED for devices that were cleaned via the (b) (4)	October 21, 2016

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	cleaning process for femoral knee implants and then distributed (see attachment 6Bi-I).	
6Bi-9	Implemented Interim Control IC-010 to address concerns about the use of (b) (4) equipment in the work center (see attachment 6Bi-G).	October 26, 2016
6Bi-10	Initiated CAPA CA-03080 to address the issues identified in Observation 6(B)(i)(a)-(b) (see attachment 6Bi-J).	December 1, 2016

Planned Actions:

No.	Action	Completion Date
6Bi-11	Conduct a root-cause analysis of the issues identified in Observation 6(B)(i) related to unapproved use of chemicals (b) (4) and equipment (b) (4)) in the femoral knee implant cleaning process.	(b) (4)
6Bi-12	Review applicable work instructions (WIG0160 and WIG00037) to identify any gaps.	(b) (4)
6Bi-13	Review cleaning operations at the Warsaw North Campus to determine whether unapproved chemicals are being used in those processes.	(b) (4)
6Bi-14	Complete HHED and initiate HHE if necessary.	(b) (4)
6Bi-15	Complete investigation (Root Cause/Action Plan) phase for CAPA CA-03080.	(b) (4)
6Bi-16	Complete action implementation phase for CAPA CA-03080, CAPA CA-02953, and CAPA CA-02645.	Target completion date to be reported in a future update
6Bi-17	Verify effectiveness of CAPA CA-03080, CAPA CA-02953, and CAPA CA-02645 and close CAPAs.	Target completion date to be reported in a future update

FDA Observation #6(B)(ii)-(v)

B. Procedures to control cleaning processes have not been adequately established. Specifically:

* * *

ii. Work instruction *WIS0086* (Rev. 3, effective 10/13/2015), which governs cleaning of sports medicine and micro fixation devices manufactured out of and materials, has not been adequately established. For example:

a. *WIS0086* instructs operators to (b) (4) ." The work instruction does not explicitly require replenishment of (b) (4)) between cycles, which was required during the original validation of this process (Validation #11, approved 10/31/1994). On 9/14/2016, we observed an operator perform this process without replenishing (b) (4) between cleaning cycles.

b. While watching the process on 9/14/2016, we observed that the ultrasonic cleaner was set to a power *(i.e.,* ultrasonic frequency) setting of (b) (4) which could be manipulated by the operator. Power setting requirements have not been defined in *WIS0086.*

Between 7/1/2014 and 10/13/2016, your firm distributed at least devices that were cleaned via this process.

iii. Work instruction *WIG0150* (Rev. 3, effective 5/5/2016), which governs (b) (4) cleaning of ultra-high-molecular-weight polyethylene (UHMWPE) devices by submersion in a bath of (b) (4) has not been adequately established. For example:

a. *WIG0150* states "DO NOT stack or allow parts to come in contact with each other." On 9/14/2016, we observed an operator pile (b) (4) devices (b) (4)) into an (b) (4) bath while performing this cleaning operation. He stated there was no limit to the amount of devices that may be placed in the bath

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and that "there's not enough room" for devices to not contact one another.

b. Your firm's Packager stated that (b) (4) baths must be dumped and refilled (b) (4). *WIG0150* indicates no such requirement, and evidence that baths are replenished as required has not been documented.

Between 7/1/2014 and 10/13/2016, your firm distributed at least (b) (4) devices that were cleaned via this process.

iv. Work instruction *WIG0035* (Rev. 4, effective 7/19/2011), which governs (b) (4) cleaning of knee femoral implants, has not been adequately established. For example, the (b) (4) cleaner is designed such that devices (b) (4) Your firm's Manufacturing Manager stated that the (b) (4) " tanks must be drained and refilled at (b) (4) *WIG0035* indicates no such requirement, and evidence that tanks are replenished as required has not been documented.

Between 7/1/2014 and 10/13/2016, your firm distributed at least (b) (4) devices that were cleaned via this process.

v. Work instruction *WIG0151* (Rev. I, effective 4/21/2015), which governs manual cleaning of metal devices, permits operators to use any of the "approved chemicals" shown in *Process Engineering Specification 1.15: Clean* (Rev. 68, effective 5/10/2016). We requested cleaning validation(s) to substantiate the use of chemicals such as (b) (4) and (b) (4) for manual metals cleaning. Your firm's Manufacturing Manager stated that those two chemicals are no longer in use by your firm and *Process Engineering Specification 1.15* has not been kept up to date.

Between 7/1/2014 and 10/13/2016, your firm distributed at least (b) (4) devices that were cleaned via this process.

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Observation 6(B)(ii)-(v) Investigation and Response:

As set forth in the below table, Zimmer Biomet initiated CAPAs to address the process control issues identified in Observation 6(B)(ii)-(v):

Observation	Issue	CAPA	Date Initiated
Observation 6(B)(ii)	Process controls for cleaning process for sports medicine and microfixation devices manufactured from (b) (4) and (b) (4) materials	CAPA CA-02855 (see attachment 6B-A, *CAPA CA-02855 Summary*)	September 15, 2016
Observation 6(B)(iii)	Process controls for cleaning process for devices made of ultra high molecular weight polyethylene ("UHMWPE")	CAPA CA-02863 (see attachment 6B-B, *CAPA CA-02863 Summary*)	September 19, 2016
Observation 6(B)(iv)	Process controls for cleaning process for knee femoral implants	CAPA CA-02953 (see attachment 6B-C, *CAPA CA-02953 Summary*)	October 12, 2016
Observation 6(B)(v)	Process controls for cleaning process for metal hip, extremities, knee, trauma, microfixation, and sports medicine devices	CAPA CA-02936 (see attachment 6B-D, *CAPA CA-02936 Summary*)	October 6, 2016

Each of the above-listed CAPAs currently is in the investigation (root cause /action plan) phase.

To contain the devices impacted by the cleaning process control deficiencies identified during the inspection (as described in Observation 6(B)(ii)-(v)), (b) (4)). To contain the sports medicine and microfixation devices manufactured out of (b) (4) and (b) (4) materials

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impacted by the cleaning validation issues identified during the inspection, Zimmer Biomet specifically also initiated (b) (4) on(b) (4) and (b) (4) both apply to the absence of an established (b) (4) power setting for the Final Clean process at work centers (b) (4) and (b) (4)).

As an additional containment measure, Zimmer Biomet (b) (4) at the following work centers associated with the process control issues: (b) (4) Zimmer Biomet also converted cleaning operations at the (b) (4) work centers from final to in-process clean work centers and the associated Manufacturing Orders ("MOs") are routed either to (b) (4) work centers for final cleaning; (b) (4) work centers have been remediated through interim controls and enhanced process monitoring. The work centers associated with the (b) (4) final cleaning process are: (b) (4)

The table below shows the last implant (non-prescription device) MO run before the production halt, and the first MO run after restart through the above final clean work centers:

Work Center #	Activity	MO #	Part #	Date	Time	Employee #
(b) (4)	Halt (b) (4))	(b) (4)	(b) (4)	09/21/2016	(b) (4)	(b) (4)
(b) (4)	Halt (b) (4))	(b) (4)	(b) (4)	09/19/2016	(b) (4)	(b) (4)
(b) (4)	Halt	(b) (4)	(b) (4)	10/11/2016	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	(b) (4)	10/20/2016	(b) (4)	(b) (4)

Work Center #	Activity	MO #	Part #	Date	Time	Employee #
(b) (4)	Halt	(b) (4)	(b) (4)	10/07/2016	(b) (4)	(b) (4)
	Restart with IC 009			10/27/2016		
(b) (4)	Halt	(b) (4)	(b) (4)	10/11/2016	(b) (4)	(b) (4)
	Restart with IC 009			10/26/2016		
(b) (4))	Halt	(b) (4)	(b) (4)	10/13/2016	(b) (4)	(b) (4)
	Restart with IC 009			10/27/2016		
(b) (4)	Halt	(b) (4)	(b) (4)	10/11/2016	(b) (4)	(b) (4)
	Restart with IC 017			11/03/2016		
(b) (4)	Halt	(b) (4)	(b) (4)	09/28/2016	(b) (4)	(b) (4)
	Restart with IC 017			10/31/2016		

The devices then were subjected to testing). Based on that testing, Zimmer Biomet took the following actions:

Observation	CAPA	CAPA Cleaning Assessment	Laboratory Test	Result	Date	Action
6(B)(ii)	CA-02855	(b) (4)	(b) (4		b) (4)	(b) (4)
6(B)(iii)	CA-02863	UHMWPE	(b) (4	(4)	b) (4)	(b) (4)
6(B)(iv)	CA-02953	(b) (4) knee	(b) (4		b) (4)	(b) (4)
6(B)(v)	CA-02936	Metals clean	(b) (4	(4)	b) (4)	(b) (4)

Observation	CAPA	CAPA Cleaning Assessment	Laboratory Test	Result	Date	Action
6(B)(v)	CA-02936	Metals (b) (4) clean (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
6(B)(v)	CA-02936	Metals (b) (4) clean (b) (4)	(b) (4)	(b) (4) (b) (b) (4)	(b) (4)	(b) (4)
6(B)(v)	CA-02936	Metals (b) (4) clean (b) (4))	(b) (4)	(b) (4)	(b) (4)	(b) (4)
6(B)(v)	CA-02936	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Zimmer Biomet will (b) (4) under the CAPA CA-02936 investigation.

The interim controls that Zimmer Biomet adopted to address the process controls issues identified in Observation 6(B)(ii)-(v) included:

- IC 002 (see attachment 6B-I, *IC 002, Revision 1, Ultra High Molecular Weight Polyethylene (UHMWPE) Final Cleaning*), which details the critical process parameters and requires documentation of these steps in the device history record ("DHR");
- IC 030 (see attachment 6B-J, *IC 030, Revision 1,* (b) (4) *for UHMWPE Final Clean*), which details (b) (4) products within the scope of IC 002;
- IC 031 (see attachment 6B-K, *IC 031, Revision 1,* (b) (4)), which details a specific (b) (4) products within the scope of IC 002;
- IC 009 (see attachment 6B-L, *IC 009, Revision 1,* (b) (4)), which prescribes the necessary manufacturing controls to ensure the effectiveness of the (b) (4) cleaning process until the process has been revalidated; and

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- IC 017 (see attachment 6B-M, *IC 017, Revision 1,* (b) (4) (b) (4) which prescribes the necessary manufacturing controls to ensure the effectiveness of the (b) (4) cleaning process until the process has been revalidated.

Going forward, Zimmer Biomet is requiring enhanced process monitoring of the Warsaw North Campus' cleaning processes to (b) (4) (b) (4) through IC 004 (see attachment 6B-O, *IC 004, Revision 1,* (b) (4) (b) (4)) until the processes are revalidated. To correct the observations in Observation 6(B)(ii)-(v), Zimmer Biomet implemented IC 014 (see attachment 6B-P, *IC 014, Revision 1,* (b) (4)), which establishes the procedure needed to conduct validations while new procedures are being established on the Warsaw North Campus and employs an approach to validation practices in which all critical process parameter specifications ("PPSs") are identified, subjected to (b) (4)), and then challenged in the validation or revalidation. Specific corrections to the particular sub-observations are as follows:

1. For Observation 6(B)(ii)(a), Zimmer Biomet will establish relevant and robust PPSs, subject each PPS to (b) (4) , and then challenge the PPS during revalidation of the (b) (4) cleaning process for sports medicine and microfixation devices made with (b) (4) and (b) (4) (see attachment 6B-Q, *ICF 014.9, Revision 3, Validation Plan)*.

2. For Observation 6(B)(ii)(b), Zimmer Biomet will establish as a PPS a (b) (4) for the (b) (4) cleaner that cannot be manipulated by the operator, subject that PPS to (b) (4) , and then challenge that PPS during revalidation of the (b) (4) cleaning process for sports medicine and microfixation devices made with (b) (4) (b) (4) (see attachment 6B-Q). It will also entail documenting the (b) (4) power setting during the revalidation as required by IC 014 (see attachment 6B-P). For example, the operational and performance qualification protocol test scripts (see attachment 6B-R, *ICF 014.10, Revision 1, OQ/PQ Protocol*), require documentation of all PPSs used throughout the execution of the validation. Lastly, the equipment will be adequately qualified per IC 014, and more specifically ICF 014.3 (see attachment 6B-S, *ICF 014.3, Revision 1, Installation Qualification Guidelines*), ICF 014.4 (see attachment 6B-T, *ICF 014.4, Revision 1, Installation Qualification*) and ICF 014.5 (see attachment 6B-U, *ICF 014.5, Revision 1, Installation Qualification Summary Report*) which will evaluate the applicable security levels and operator interface of the Final Cleaning equipment.

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3. For Observation 6(B)(iii)(a), Zimmer Biomet will determine whether prohibiting parts from coming into contact with each other in the (b) (4) bath is a PPS, subject that PPS to (b) (4), and then challenge that PPS during revalidation of the (b) (4) cleaning process for UHMWPE devices. Prior to revalidation, controls have been put in place through IC 002 (see attachment 6B-I) that limit the maximum number of pieces per bath, and prohibit contact between the pieces.

4. For Observation 6(B)(iii)(b), Zimmer Biomet will determine whether a requirement to (b) (4) is a PPS, subject that PPS to (b) (4) and then challenge that PPS during revalidation of the (b) (4) cleaning process for UHMWPE devices. Prior to revalidation, controls have been put in place through IC 002 that require (b) (4) (b) (4) with (b) (4). This change of (b) (4) is documented on a controlled form ICF 002.3 (see attachment 6B-V, *ICF 002.3, Revision 1,* (b) (4) (b) (4)).

5. For Observation 6(B)(iv), Zimmer Biomet will establish relevant and robust PPS, subject the PPS to (b) (4), and then challenge the PPS during revalidation of the (b) (4) cleaning process for knee femoral implants (see attachment 6B-Q).

6. For Observation 6(B)(v), Zimmer Biomet implemented a procedure that requires (a) that manufacturing materials used in production cells (b) (4) and attachment (b) (4) For Observation 6(B)(v), Zimmer Biomet will convert the (b) (4) cleaning process used to clean metal hip, extremities, knee, and trauma devices to (b) (4) cleaning which will be followed or replaced by an (b) (4) final cleaning. This final cleaning process will then be validated so that approved chemicals and materials approved for use in the cleaning process are part of the validation. In addition, Zimmer Biomet will update the associated Process Engineering Specifications to reflect the chemicals approved for such cleaning.

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Zimmer Biomet will conduct investigations pursuant to CAPA CA-02855, CAPA CA-02863, CAPA CA-02953, and CAPA CA-02936 that include the following tasks:

1. Pursuant to CAPA CA-02855, conduct a root-cause analysis of the issues identified in Observation 6(B)(ii);
2. Develop an implementation plan for CAPA CA-02855;
3. Develop a verification of effectiveness ("VoE") plan for CA-02855;
4. Pursuant to CAPA CA-02863, conduct a root-cause analysis of the issues identified in Observation 6(B)(iii);
5. Develop an implementation plan or CAPA CA-02863;
6. Develop a VoE plan for CAPA CA-02863;
7. Pursuant to CAPA CA-02953, conduct a root-cause analysis of the issues identified in Observation 6(B)(iv);
8. Develop an implementation plan for CAPA CA-02953;
9. Develop a VoE plan for CAPA CA-02953;
10. Pursuant to CAPA CA-02936, conduct a root-cause analysis of the issues identified in Observation 6(B)(v);
11. Develop an implementation plan for CAPA CA-02936; and
12. Develop a VoE plan for CAPA CA-02936.

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The health hazard evaluation determinations ("HHED") initiated by Zimmer Biomet to evaluate the products distributed between July 1, 2014, and October 13, 2016 and the resulting health hazard evaluations ("HHE") are summarized in the table below:

Scope	HHED#, Completion Date	HHED Conclusion	HHE#, Completion Date	HHE Recommendation
At least (b) (4) devices that were cleaned via the (b) (4) cleaning process for sports medicine and microfixation devices made with (b) (4)	HHED 09-2016-096 (attachment 6B-Y, *HHED 09-2016-096*), completed on September 30, 2016	(b) (4)	HHE 2016-211 (attachment 6B-CC, *HHE 2016-211*), completed on December 15	(b) (4)
At least (b) (4) devices that were cleaned via the (b) (4) cleaning process for UHMWPE devices	HHED 10-2016-035 (attachment 6B-Z, *HHED 10-2016-035*), completed on October 27, 2016	(b) (4)	HHE 2016-236 (attachment 6B-DD, *HHE 2016-236*), completed on December 16, 2016	(b) (4)
At least (b) (4) devices that were cleaned via the (b) (4) cleaning process for knee femoral implants	HHED 10-2016-038 (attachment 6B-AA, *HHED 10-2016-038*) completed on October 13, 2016	(b) (4)	HHE 2016-258 (attachment 6B-EE, *HHE 2016-258*), completed on December 16, 2016	(b) (4)
At least (b) (4) devices that were cleaned via the (b) (4) cleaning process used to clean metal hip, extremities, knee, and trauma devices	HHED 10-2016-037 (attachment 6B-BB, *HHED 10-2016-037*), completed on November 15, 2016	(b) (4)	HHE 2016-257 (attachment 6B-FF, *HHE 2016-257*), completed on December 18, 2016	(b) (4)

HHE 2016-257: The toxicology review (b) (4) . The clinical performance based on complaints, literature, and registries were reviewed (b) (4) . (b) (4) .

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Completed Actions:

No.	Action	Completion Date
6B-1	Initiated CAPA CA-02855 (see attachment 6B-A).	September 15, 2016
6B-2	Initiated CAPA CA-02863 (see attachment 6B-B).	September 19, 2016
6B-3	Halted cleaning operations at the following work centers: (b) (4)	September 21, 2016
6B-4	Initiated (b) (4)	September 22, 2016
6B-5	Initiated (b) (4)	September 27, 2016
6B-6	Initiated HHED 09-2016-096 (see attachment 6B-Y).	September 30, 2016
6B-7	Initiated CAPA CA-02936 (see attachment 6B-D).	October 6, 2016
6B-8	(b) (4) (b) (4) (b) (4) (b) (4)).	October 11, 2016
6B-9	Initiated CAPA CA-02953 (see attachment 6B-C).	October 12, 2016
6B-10	Initiated (b) (4)	October 12, 2016
6B-11	Subjected UHMWPE devices (b) (4)	October 12, 2016
6B-12	(b) (4) (b) (4)	October 13, 2016
6B-13	Initiated HHED 10-2016-038 (see attachment 6B-AA).	October 13, 2016
6B-14	Subjected (b) (4)	October 16, 2016
6B-15	Implemented IC 002 to prescribe the necessary manufacturing controls to ensure the effectiveness of the UHMWPE final cleaning process until the process has been revalidated (see attachment 6B-I).	October 26, 2016
6B-16	Required enhanced process monitoring of the Warsaw North Campus' cleaning processes to (b) (4) cleaning standards until the processes are revalidated through IC 004 (see attachment 6B-O).	October 20, 2016
6B-17	Implemented interim control form to document change of (b) (4) (see attachment 6B-V).	October 21, 2016
6B-18	Subjected (b) (4) devices placed on quality hold to (b) (4) testing and, based on the testing, released them from the hold (see attachment 6B-H).	October 24, 2016
6B-19	Subjected (b) (4) (b) (4)	October 25, 2016
6B-20	Implemented IC 009 to prescribe necessary manufacturing controls to	October 26, 2016

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No.	Action	Completion Date
	ensure the effectiveness of the (b) (4) cleaning process until the process has been revalidated (see attachment 6B-L).	
6B-21	Initiated HHED 10-2016-035 (see attachment 6B-Z).	October 27, 2016
6B-22	Implemented IC 017 to prescribe the necessary manufacturing controls to ensure the effectiveness of the (b) (4) final cleaning process until the process has been revalidated (see attachment 6B-M).	October 31, 2016
6B-23	Implemented IC 014, and associated Interim Control Forms to establish the procedure needed to conduct validations while new procedures are being established on the Warsaw North Campus and to address PPS issues (see attachments 6B-P, 6B-R, 6B-S, 6B-T, and 6B-U).	November 1, 2016
6B-24	Subjected (b) (4) (b) (4)	November 3, 2016
6B-25	(b) (4)	November 7, 2016
6B-26	(b) (4) , based on the testing, continued the hold (see attachment 6B-H).	November 8, 2016
6B-27	Implemented SOP 9.0.1 and Manufacturing Materials – Master List to require (a) that manufacturing materials used in production cells be documented and (b) that a formal request be submitted in order to introduce new manufacturing materials into the production cell (see attachment 6B-W and attachment 6B-X).	November 8, 2016
6B-28	Completed HHED 10-2016-037 (see attachment 6B-BB).	November 15, 2016
6B-29	Implemented IC 030 which details pre-cleaning for over-molded products within the scope of IC 002 (see attachment 6B-J).	November 30, 2016
6B-30	Implemented IC 031 which details a specific (b) (4) for (b) (4) products within the scope of IC 002 (see attachment 6B-K).	November 30, 2016
6B-31	Subjected (b) (4) (b) (4)	December 2, 2016
6B-32	Revised interim control form for Validation Plan under IC 014 (see attachment 6B-Q).	December 8, 2016
6B-33	Completed HHE 2016-211 (see attachment 6B-CC)	December 15, 2016
6B-34	Completed HHE 2016-236 (see attachment 6B-DD)	December 16, 2016
6B-35	Completed HHE 2016-258 (see attachment 6B-EE)	December 16, 2016
6B-36	Completed HHE 2016-257 (see attachment 6B-FF)	December 18, 2016

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Planned Actions:

No.	Action	Completion Date
6B-37	Pursuant to CAPA CA-02855, conduct a root-cause analysis of the issues identified in Observation 6(B)(ii).	(b) (4)
6B-38	Complete Root Cause /Action Plan Phase for CA-02855.	(b) (4)
6B-39	Develop an implementation and VoE plan for CA-02855.	Target completion date to be reported in a future update
6B-40	Pursuant to CAPA CA-02863, conduct a root-cause analysis of the issues identified in Observation 6(B)(iii).	(b) (4)
6B-41	Complete Root Cause /Action Plan Phase for CA-02936.	(b) (4)
6B-42	Develop an implementation and VoE plan for CAPA CA-02936.	Target completion date to be reported in a future update
6B-43	Pursuant to CAPA CA-02953, conduct a root-cause analysis of the issues identified in Observation 6(B)(iv).	(b) (4)
6B-44	Complete Root Cause /Action Plan Phase for CA-02953.	(b) (4)
6B-45	Develop an implementation and VoE plan for CAPA CA-02953.	Target completion date to be reported in a future update
6B-46	Pursuant to CAPA CA-02936, conduct a root-cause analysis of the issues identified in Observation 6(B)(v).	(b) (4)
6B-47	Complete Root Cause /Action Plan Phase for CA-02863.	(b) (4)
6B-48	Develop an implementation and VoE plan for CAPA CA-02863.	Target completion date to be reported in a future update

FDA Observation 6(C)

C. Your firm's Storage of (b) (4) Process Engineering Specification (PES) 9.14, Rev. 10 effective 07/25/2016, is inadequate in that controls necessary for ensuring LactoSorb product quality during manufacturing operations have not been adequately established. While observing machining operations for LactoSorb (b) (4) mm x (b) (4) mm screws, item (b) (4) lot #M540870, we found that the degree of exposure to uncontrolled environments varies greatly from the first device manufactured in the lot to the last device. Section 4.2.3 of PES 9.14 states (b) (4) " Interviews with the operator revealed:

i. Each machined screw is placed onto a tray on the work bench where they stay until the lot is completed. The tray is open, exposed to an uncontrolled environment, and contains no desiccant.

ii. Operation 0020, "Machine to Print," had been running for (b) (hours and was still in-process at the time of the interview.

iii. The finished lot quantity was (b) (4) screws. According to your firm's (b) (4) system, the minimum amount of time needed to manufacture (b) (4) screws would be (b) (4) hours.

Your firm's subject matter experts have indicated that LactoSorb devices are moisture-sensitive and can experience degradation with prolonged exposure to humidity in the environment.

Observation 6(C) Investigation and Response:

On December 1, 2016, Zimmer Biomet opened CAPA CA-03081 to investigate and address the findings in Observation 6(C) regarding inadequate process controls for in-process product made from LactoSorb (see attachment 6C-A, *CAPA CA-03081 Summary*). CA-03081 is currently in the CAPA Investigation (Root Cause/Action Plan) Phase.

Observation 6(C) concerns the control of environmental exposure during the manufacturing process of devices manufactured from LactoSorb. (b) (4) The FDA investigators observed that screws

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machined from LactoSorb were placed on a tray on a work bench during the machining of an entire lot of screws (b) (4) screws), exposed to the uncontrolled work environment.

A Process Engineering Specification ("PES") outlines the storage requirements for LactoSorb product during the manufacturing process (see attachment 6C-B*, Process Engineering Specification 9.14*—(b) (4) *(Rev. 10)*). As identified in Observation 6(C), PES 9.14 does not contain sufficient process controls for ensuring LactoSorb product quality during manufacturing operations. (b) (4) of PES 9.14 requires operators to (b) (4) Zimmer Biomet has preliminarily determined that (b) (4)

(b) (4) of PES 9.14 does specify that all product is to be stored eithe (b) (4) These specific storage conditions for long-term and short-term storage are controlled environments which serve to minimize the long-term exposure to the uncontrolled environment. (b) (4) Pressure, temperature and concentration are examples of those system variables. (b) (4)

During the FDA inspection, on September 26, 2016, upon identification of the issue, Zimmer Biomet (b) (4)

(b) (4) until full assurance all containment activities have been completed, including review of manufacturing, cleaning and sterilization processes. Finally, , Zimmer Biomet opened Health Hazard Evaluation Determination ("HHED") #12-2016-008 to evaluate the potential impact to patients and to determine the need to conduct a Health Hazard Evaluation ("HHE") (see attachment 6C-E, *HHED 12-2016-008*). (b) (4)

In addition to the containment actions described in the preceding paragraph, under CAPA CA-03081, Zimmer Biomet has begun investigating the issues regarding exposure of LactoSorb products to the uncontrolled environment within Warsaw North Campus. The investigation has included a review (b) (4) as well as an investigation to evaluate the potential impact of exposure to the uncontrolled environment.

- (b) (4)

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- (b) (4)
- (b) (4)
- (b) (4)

Additionally, as mentioned above and per PES 9.14, between each manufacturing process step, (b) (4) . Therefore, returning the

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LactoSorb material (b) (4) .

Given the analysis of the impact of (b) (4) on in-process LactoSorb material, the lot release (b) (4) data, and the (b) (4) storage conditions between manufacturing steps, Zimmer Biomet is confident that exposure to the uncontrolled work environment does not cause the LactoSorb product to degrade in an appreciable manner or in a way that would result in product that does not meet specifications. Zimmer Biomet is committed to fully investigating the issue and intends to implement any corrective actions found to be necessary as a result of the investigation under CAPA CA-3081.

Further investigation as it relates to CAPA CA-3081 will include:

1. Completing root cause investigation; and
2. Completing Investigation (Root Cause/Action Plan) Phase of CAPA.

Completed Actions:

No.	Action	Completion Date
6C-1	Initiated (b) (4) for (b) (4) Sterilization (see attachment 6C-C).	September 20, 2016
6C-2	Initiated (b) (4) (b) (4)	September 22, 2016
6C-3	Conducted an investigation to characterize the (b) (4) of (b) (4) product following exposure to the manufacturing environment (see attachment 6C-H).	October 3, 2016
6C-4	Conducted review of (b) (4) deviations for (b) (4) Product (see attachment 6C-J(i) and attachment 6C-J(ii).	November 2, 2016
6C-5	Initiated CAPA CA-03081 to address the issues identified in Observation 6(C) (see attachment 6C-A).	December 1, 2016
6C-6	Opened HHED #12-2016-008 to evaluate the potential impact to patients and to determine the need to conduct a Health Hazard Evaluation ("HHE") (see attachment 6C-E).	December 1, 2016
6C-7	Conducted an analysis of (b) (4) (b) (4) (see attachment 6C-I).	December 9, 2016

Planned Actions:

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No.	Action	Completion Date
6C-8	Review exposure times for in-process LactoSorb material at each process step for each of (b) (4) process flows for LactoSorb products and calculate (b) (4)	(b) (4)
6C-9	Review data from the study of exposure times for in-process LactoSorb material and compare it to existing (b) (4) data.	(b) (4)
6C-10	Review the exposure conditions ((b) (4)) for each step in each of (b) (4) manufacturing process flows.	(b) (4)
6C-11	Review relevant process documents, including PES 9.14, to clarify the storage conditions and exposure time limits.	(b) (4)
6C-12	Review the qualification of (b) (4)	(b) (4)
6C-13	Conduct statistical review of the data to determine if the current sampling plant is sufficient or if an Interim Control is required.	(b) (4)
6C-14	Complete Root Cause/Action Plan Phase	(b) (4)
6C-15	Complete CA-03081 Action Implementation Phase.	Target completion date to be reported in a future update
6C-16	Verify effectiveness of CA-03081 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation 7

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FDA Observation #7

Procedures for monitoring and control of process parameters for a validated process have not been adequately established.

Observation 7 Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03083 to address the findings regarding process monitoring for validated processes as exemplified by Observations 7(A) and 7(B) (see attachment 7-A, *CAPA CA-03083 Summary*). Also on December 1, 2016, Zimmer Biomet initiated CAPA CA-03084 to address the finding in Observation 7(C) regarding the failure to follow a defined sampling plan due to delays at (b) (4) (see attachment 7-B, *CAPA CA-03084 Summary*). Both CAPA CA-03083 and CAPA CA-03084 are currently in the Investigation (Root Cause/Action Plan) Phase.

As an initial process containment action, (b) (4) during the course of the recent FDA inspection between September 19, 2016 and October 13, 2016, in response to issues observed by the FDA investigators (b) (4) (b) (4) until the implementation of Interim Control IC-004 on October 20, 2016, which applies the process monitoring controls for final clean processes validated prior to the initiation of the Interim Control (see attachment 7-D, *IC 004* (b) (4), Rev. 1, and Training Records). IC-004 describes the necessary process monitoring requirements to ensure product cleanliness is maintained to pre-determined Zimmer Biomet requirements, until the cleaning processes can be re-validated. Under IC-004, worst-case parts are identified using the following criteria: (b) (4) This rationale for worst-case part selection is documented and approved per form ICF-004.1 (see attachment 7-E, *ICF-004.1*). Finally, under IC-004, once normal distribution of the variable data is confirmed, (b) (4) of the process at issue is calculated with summary statistics for each characteristic for product cleanliness defined in IC-004. If Normality cannot be achieved, then a data transformation is pursued. (b) (4)

In addition to the process containment achieved by the implementation of Interim Control IC-004, (b) (4), implemented during the inspection on September 29, 2016 and October 12, 2016 respectively (b) (4)

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(b) (4)

As an initial corrective action taken in response to the Observation 7 findings regarding process monitoring, Zimmer Biomet implemented SOP 9.3.4, *Process Monitoring of Validated Processes*, Rev. 1 during the inspection on November 8, 2016 (see attachment 7-H, *SOP 9.3.4 Process Monitoring of Validated Processes, Rev 1, and Training Records*). SOP 9.3.4 applies to all validated processes and defines the requirements for process monitoring of outputs of validated processes. The procedure provides instructions for: (1) launching investigations when sample test results fall outside of specification or exhibit unexpected process trends; and (2) establishing and maintaining variable sampling and monitoring plans used to monitor the outputs of validated processes. Specifically, in the event that the sample mean or standard deviation falls outside of the defined Process Control Limit(s), or if the test results are out of specification, an investigation of the process is required. The investigation tasks to be followed are defined in Section 7.12.2 of IC-004. Finally, under SOP 9.3.4, all required testing must be completed, results must be trended for ongoing process control, and all required investigations must be completed and documented.

Under CAPA CA-03083, Zimmer Biomet will evaluate all procedures, forms, and work instructions associated with process monitoring to ensure that the quality system is compliant with the requirements of 21 C.F.R. § 820.75(b). Specifically, Zimmer Biomet will ensure that procedures, forms, and work instructions address the following deficiencies identified in Observation 7:

1. The determination of an appropriate sampling plan for monitoring a validated process;

2. The selection of appropriate samples for monitoring a validated process, including the use of simulated product and justification that simulated product represents an equal or greater challenge than the most difficult product in the process; and

3. The process for ensuring the timely review and analysis of data obtained a defined sampling plan conducted for process monitoring activities.

Zimmer Biomet will revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of each of the foregoing process monitoring requirements for all validated processes, and to ensure compliance with the requirements of 21 C.F.R. § 820.75(b). Specific

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revisions will be identified following the completion of the Investigation (Root Cause/Action Plan) Phase of CAPA CA-03083, which will include:

1. Completion of a root cause analysis scoped to include the issues identified in Observations 7(A), 7(B), and 7(C) and any other process monitoring requirements;
2. Identification of procedures that define sample size selection and worst-case product selection for process monitoring. In addition to driving revisions, as needed, to existing procedures, forms, and work instructions, the outcome of these investigation steps will inform a reassessment of the need to implement any additional containment actions to address any process monitoring deficiencies. Zimmer Biomet will provide details regarding actions identified as a result of the investigation conducted under CAPA CA-03083 in future updates to this response.

In addition to these system-wide actions, Zimmer Biomet will take specific actions to identify and implement appropriate corrections and corrective actions to address the findings regarding sampling plans for processing monitoring of cleaning processes identified in Observation 7(A), the use of simulants identified in Observation 7(B), and adherence to the sampling plan identified in Observation 7(C); those specific actions are discussed in further detail in the applicable sub-sections of this response.

Completed Actions:

No.	Action	Completion Date
7-1	Implemented (b) (4) for product in inventory at Zimmer Biomet (b) (4)	September 29, 2016
7-2	(b) (4)	October 13, 2016
7-3	Implemented Interim Control IC-004 adding increased process monitoring requirements (see attachment 7-D).	October 20, 2016
7-4	Implemented (b) (4)	October 12, 2016
7-5	Implemented SOP 9.3.4, *Process Monitoring of Validated Processes*, Rev. 1 to contain directions regarding the development and documentation of statistically justified sampling plans for process monitoring and to require the selection of sample size based on (b) (4)	November 8, 2016
7-6	Initiated CAPA CA-03083 to address the issues identified in Observation 7 with respect to process monitoring (see attachment 7-A).	December 1, 2016

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Planned Actions:

No.	Action	Completion Date
7-7	Identify process monitoring activities in use at the Warsaw North Campus.	(b) (4)
7-8	Determine if any additional containment is required following completion of root cause analysis.	(b) (4)
7-9	Complete CAPA CA-03083 Investigation (Root Cause/Action Plan) Phase.	(b) (4)
7-10	Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of statistical rationales for sampling plans.	Target completion date to be reported in a future update
7-11	Complete CAPA CA-03083 Implementation Phase.	Target completion date to be reported in a future update
7-12	Verify effectiveness of CAPA CA-03083 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #7A

Specifically,

Note: This is a repeat observation from the FDA inspection dated 6/16/2014 to 6/30/2014.

A. Valid statistical rationale for the sampling plans used has not been documented. *QP0026* requires the following number of samples to be tested on a (b) (4) basis:
i. (b) (4)

Observation 7A Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03083 to address the issue identified in Observation 7(A) concerning the statistical rationale for sampling plans for cleaning process monitoring. CAPA CA-03083 is currently in the Investigation (Root Cause/Action Plan) Phase (see attachment 7-A, *CAPA CA-03083 Summary*). CAPA CA-03083 also addresses the finding in Observation 7(B) concerning the use of simulants for process monitoring, as well as process monitoring activities

The initial process and(b) (4) actions for process monitoring are described above in the response to Observation 7. These actions include: (1) the institution of (b) (4) (3) the implementation of Interim Control IC-004 implementing increased process monitoring activies, and (4) the implementation of SOP 9.3.4, *Process Monitoring of Validated Processes*, Rev. 1, establishing sampling plan requirements and launching investigations for validated processes (see attachment 7-D, *IC 004 Process Monitoring of Final Cleaning*, Rev. 1, and Training Records, attachment 7-F, *QH16-064,* attachment 7-G, *QH16-068, and* attachment 7-H, *SOP 9.3.4 Process Monitoring of Validated Processes, Rev 1, and Training Records*).

These process monitoring containment actions are applicable to the cleaning process monitoring activities identified in Observation 7(A). With respect to the determination of sample size for process monitoring of cleaning processes specifically, per section 7.2.5 of Interim Control IC-004, *Process Monitoring Of Final Cleaning* (see attachment 7-D), These statistically based plans are determined using a variable sampling plan contained in Appendix B of IC-004. The selected plan is identified by completing Form ICF-004.1, which allows the user

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to determine the appropriate sampling plan based (b) (4) (see attachment 7-E, *ICF-004.1*). Additionally, SOP 9.3.4, *Process Monitoring of Validated Processes*, Rev. 1, implemented on November 8, 2016, contains provisions regarding the development and documentation of statistically justified sampling plans for process monitoring (see attachment 7-H). Specifically, section 7.5 requires that sample size be selected based on (b) (4)

As an immediate correction for finding in Observation 7(A), (QP0026, (b) (4) Rev. 6 does not have an adequately justified and documented statistical rationale for the selected number of samples to be tested on a (b) (4) basis), Zimmer Biomet has implemented Interim Control IC-004, *Process Monitoring Of Final Cleaning* which requires statistically based sampling (see attachment 7C-B, QP0026 (b) (4) *6*). With respect to the example in Observation 7(A)(i) and Observation 7(A)(ii), Zimmer Biomet has implemented interim control IC-004 as described in the preceding paragraph and in the response to Observation 7 for all (b) (4) clean processes to replace QP0026.

Under CAPA (b) (4)

In addition to the work on process monitoring being performed under Observations 7, 7(A), 7(B), and 7(C), (b) (4) These actions are being implemented under CAPA CA-03083.

Completed Actions:

No.	Action	Completion Date
7A-1	Implemented interim control IC-004 and form ICF-004.1 to guide selection of valid statistical samples (b) (4) (see attachment 7-D and 7-E).	October 20, 2016
7A-2	Implemented SOP 9.3.4, *Process Monitoring of Validated Processes*, Rev. 1 regarding the development and documentation of statistically justified sampling plans for process monitoring and to require the	November 8, 2016

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	selection of sample size (b) (4) (see attachment 7-H).	
7A-3	Initiated CAPA CA-03083 to address the issues identified in Observation 7(A) (see attachment 7-A).	December 1, 2016

Planned Actions:

No.	Action	Completion Date
7A-4	Identify any procedures that define sample size selection for process monitoring across the Warsaw North Campus.	(b) (4)
7A-5	Determine if additional containment actions are necessary following the completion of the root cause analysis and review of sampling plans in process monitoring procedures.	(b) (4)
7A-6	Determine if the statistical rationale is available and justified for all sampling plans identified in process monitoring procedures across the Warsaw North Campus.	(b) (4)
7A-7	Complete CAPA CA-03083 Investigation (Root Cause/Action Plan) Phase.	(b) (4)
7A-8	Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of statistical rationales for sampling plans.	Target completion date to be reported in a future update
7A-9	Complete CAPA CA-03083 Implementation Phase.	Target completion date to be reported in a future update
7A-10	Verify effectiveness of CAPA CA-03083 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #7(B)

A. Two of the (b) (4) processing lines accounted for by your sampling plan utilize simulated product (part number CP550157). Adequate justification that the simulated product represents an equal or greater challenge than the most difficult to clean metallic device manufactured via these processing lines has not been documented. Notably, your firm's Engineering Manager explained that acetabular cups are the worst-case devices that are processed through the (b) (4) cleaning process in part due to the devices' large porous surface area. The porous surface area calculated for the 80mm acetabular cup with part number 14-104080 ((b) (4) is approximately (b) (4) % larger than the porous surface area of the simulated product CP550157 used during cleaning process monitoring (b) (4)).

Observation 7(B) Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03083 to investigate and address the issues identified in Observation 7(B) concerning the use of simulated product in cleaning and (b) (4) lines at the Warsaw North Campus (see attachment 7-A, *CAPA CA-03083 Summary*). CAPA CA-03083 is currently in the Investigation (Root Cause/Action Plan) Phase.

As explained in the response to Observation 7 above, Zimmer Biomet has taken several steps to address process monitoring of cleaning processes across the Warsaw North Campus. Those actions include the initiation of CAPA CA-03083, the implementation of Interim Control IC-004, the institution of (b) (4), and the implementation of SOP 9.3.4, *Process Monitoring of Validated Processes*, Rev. 1 (see attachment 7-D, *IC 004 Process Monitoring of Final Cleaning*, Rev. 1, and Training Records, attachment 7-F, *QH16-064,* and attachment 7-H, *SOP 9.3.4 Process Monitoring of Validated Processes, Rev 1, and Training Records*). Each of those actions, as they address process monitoring as a whole, are discussed in the response to Observation 7, above. The investigation and identification and implementation of corrective actions with respect to the use of simulated product for cleaning process monitoring activities identified in Observation 7(B) will also occur under CAPA CA-03083, as discussed in this section.

During the inspection, on October 20, 2016 Zimmer Biomet discontinued the use of simulants for process monitoring for final cleaning processes (see attachment 7-D). Under Interim Control IC-004, worst-case parts are used for process monitoring of final cleaning processes in place of simulants, using the following criteria for selection of the worst-case parts: (b) (4) This rationale for worst-case part selection is documented and approved per form ICF-004.1 (see attachment 7-E, *ICF-004.1*). IC-004 has

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been applied to all final clean processes at Warsaw North Campus for the selection of worst-case parts for process monitoring, and appropriate personnel were trained to the requirements of IC-004 (see attachment 7-D). All product that is cleaned in the (b) (4) Cleaning process identified in Observation 7(B) is cleaned and monitored as part of IC-009, (b) (4) for which Zimmer Biomet replaced the simulated product actual product for worst-case process monitoring samples (see attachment 7B-A, Completed (b) (4)). In addition, Zimmer Biomet implemented Interim Controls for final cleaning processes at the Warsaw North Campus to ensure appropriate manufacturing controls are in place for each specific cleaning process.

Further, Section 7.1.1 of IC-004 requires worst-case parts to be identified (b) (4) for process monitoring of final cleaning processes.

As referenced in the response to Observation 7, all product cleaned through processes that previously used simulants (b) (4) During the investigation conducted under CAPA CA-03083, Zimmer Biomet will determine whether any additional containment actions (b) (4) are warranted. Zimmer Biomet will provide information regarding such containment actions, if any, in future updates to this response.

The investigation conducted under CAPA CA-03083 will also determine whether simulated product is used for process monitoring of any additional processes at the Warsaw North Campus, in addition to those cleaning processes covered Interim Controls IC-004. Zimmer Biomet will also determine if documented justifications are available for the identification and selection of worst-case product for all process monitoring activities at Warsaw North Campus, beyond QP0026 which is identified in Observation 7(B) (see attachment 7C-B, QP0026 (b) (4) (b) (4) *Rev 6*). Further, under IC-004, once normal distribution of the variable data is confirmed, (b) (4) of the process at issue is calculated (b) (4) Prior to beginning the Implementation Phase of CAPA CA-03083, Zimmer Biomet will determine what corrective actions are necessary to address any additional instances of simulant use found during the investigation of CAPA CA-03083; details regarding any such actions will be provided in a future update to this response.

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Completed Actions:

No.	Action	Completion Date
7B-1	(b) (4)	September 29, 2016
7B-2	Implemented and trained to IC-004. Discontinued the use of simulants for process monitoring for final cleaning processes and implemented use of actual products instead under section 7.1.1 of Interim Control IC 004 (see attachment 7-D).	October 20, 2016
7B-3	Implemented (b) (4)	October 12, 2016
7B-4	Initiated CAPA CA-03083 to address the issues identified in Observation 7(B) (see attachment 7-A).	December 1, 2016

Planned Actions:

No.	Action	Completion Date
7B-5	Conduct root cause analysis for CAPA CA-03083 and issues identified in Observation 7(B).	(b) (4)
7B-6	Determine if documented justification is available for sampling plans demonstrating the use of the worst-case samples for all process monitoring activities at Warsaw North Campus other than QP0026.	(b) (4)
7B-7	Identify any additional occurrences of the use of simulated product for process monitoring at the Warsaw North Campus.	(b) (4)
7B-8	Complete CAPA CA-03083 Investigation (Root Cause/Action Plan) Phase	(b) (4)
7B-9	Complete CAPA CA-03083 Implementation Phase.	Target completion date to be reported in a future update
7B-10	Verify effectiveness of CAPA CA-03083 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #7(C)

C. The defined sampling plan has not been followed because, as explained by your firm's manufacturing Manager and Senior Director of Research, your (b) (4) (b) (4) is six months behind schedule due to a backlog of samples requiring testing. For example, as of 9/12/2016, your firm was unable to provide evidence that total carbon residue testing had been performed for:

i. Devices manufactured more recently than 5/25/2016 via 4 of the (b) (4) processing lines:
- **i. Devices processed through the (b) (4) cleaning process and line(s)**
- **ii. Devices processed through the (b) (4) cell cleaning process and (b) (4) line**
- **iii. Oxford knee tibial tray components**
- **iv. Oxford knee femoral components**

Between 5/26/2016 and 9/9/2016, (b) (4) devices were manufactured via these processing lines. (b) (4) devices have been distributed as of 9/9/2016.

ii. Devices manufactured more recently than 2/8/2016 via 2 of the processing lines:
- **i. Devices processed through the (b) (4) cleaning (b) (4) lines" (Work Center (b) (4))**
- **ii. Devices manufactured in (b) (4)**

Between 2/9/2016 and 9/9/2016, (b) (4) devices were manufactured via these processing lines. (b) (4) devices have been distributed as of 9/9/2016.

iii. Devices manufactured more recently than 5/2/2016 via the (b) (4) cleaning process and (b) (4) line." Between 5/3/2016 and 9/9/2016, (b) (4) devices were manufactured via this processing line. (b) (4) of the (b) (4) devices have been distributed as of 9/9/2016.

iv. Trauma products manufactured more recently than 4/26/2016 via the (b) (4) cleaning process and (b) (4) line. Between 4/27/2016 and 9/9/2016,

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(b) (4) **devices were manufactured via this processing line.** (b) (4) **of the devices have been distributed as of 9/9/2016.**

Observation 7(C) Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03084 to address issues related to the monitoring and control of process parameters for validated processes identified in Observation 7(C) (see attachment 7-B, *CAPA CA-03084 Summary*). CAPA CA-03084 is currently in the Investigation (Root Cause/Action Plan) Phase.

In September 2016, in response to the the ongoing FDA inspection, (b) (4) at the Warsaw North Campus. On October 20, 2016, Zimmer Biomet implemented Interim Control IC-004 (see attachment 7-D, *IC 004 Process Monitoring of Final Cleaning*, Rev. 1, and Training Records), which applies (1) process monitoring controls (2) final clean processes from Zimmer Biomet which were validated prior to the initiation of the interim control. IC-004 has replaced QP0026 for all final clean process monitoring, (b) (4) .

IC-004 describes the process monitoring requirements that are needed to ensure that product cleanliness is maintained to pre-determined Zimmer Biomet requirements until cleaning processes can be re-validated. Under IC-004, worst-case parts are identified using the following criteria: (b) (4) The rationale for worst-case part selection is documented and approved per form ICF-004.1 (see attachment 7-E, *ICF-004.1*). (b) (4) Zimmer Biomet trained appropriate personnel to the requirements of IC-004 (see attachment 7-D).

(b) (4) .

To further correct the issues identified in Observation 7(C), Zimmer Biomet implemented standard operating procedure ("SOP") 9.3.4, *Process Monitoring of Validated Processes* (Rev. 1) during the inspection on November 8, 2016 (see attachment 7-H, *SOP 9.3.4 Process Monitoring of Validated Processes, Rev 1, and Training Records*). SOP 9.3.4 applies to all validated processes and defines the requirements for process monitoring of outputs of validated

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processes. The procedure provides instructions for: (1) launching investigations when sample test results fall outside of specification or exhibit unexpected process trends and (2) establishing and maintaining variable sampling and monitoring plans used to monitor the outputs of validated processes. The investigation tasks to be followed are defined in Section 7.12.2 of IC-004. Further, under IC-004, worst-case parts are identified using the following criteria: (b) (4) This rationale for worst-case part selection is documented and approved per form ICF-004.1. Additionally, under IC-004, once Normality is confirmed, (b) (4) defined in IC-004. Finally, under SOP 9.3.4, all required testing must be completed, with results entered into the appropriate software system, and all required investigations must be completed and documented.

Completed Actions:

No.	Action	Completion Date
7C-1	(b) (4) .	September 2016
7C-2	Implemented Interim Control IC-004 (see attachment 7-D).	October 20, 2016
7C-3	Trained appropriate personnel on the requirements of IC-004 (see attachment 7-D).	October 20 – November 1, 2016
7C-4	Implemented SOP 9.3.4 (see attachment 7-H).	November 8, 2016
7C-5	Initiated CAPA CA-03084 to address issues related to the monitoring and control of process parameters for a validated processes identified in Observation 7(C) (see attachment 7-B).	December 1, 2016
7C-6	Completed al (b) (4) (see attachment 7C-A).	December 19, 2016

Planned Actions:

No.	Action	Completion Date
7C-7	Identify process monitoring at the Warsaw North Campus other than QP0026.	(b) (4)
7C-8	Conduct a root-cause analysis of the issues identified in Observation 7(C), (b) (4) and any other process monitoring requirements across the Warsaw North Campus.	(b) (4)
7C-9	(b) (4) for QP0026 and any additional process monitoring across the campus.	(b) (4)
7C-10	Determine if additional test laboratory testing capacity is required to sustain ongoing QP0026 and any additional process monitoring across the campus.	(b) (4)
7C-11	Complete CAPA CA-03084 Investigation (Root Cause/Action Plan) Phase	(b) (4)

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7C-12	Complete CAPA CA-03084 Implementation Phase.	Target completion date to be reported in a future update
7C-13	Verify effectiveness of CAPA CA-03084 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation 8

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FDA Observation #8

Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been adequately established.

Specifically,

A. Procedures for populating the "Complaint Category" field in complaint files have not been adequately established; as a result, complaints are not categorized in a consistent manner. Your firm's Post Market Surveillance Manager explained that the Complaint Category field is used for trending complaint data during (b) (4) CAPA Meetings." He confirmed that a quality system procedure does not exist that describes the categories that may be selected and when they shall be used. Consequently, your firm's complaint data under-represents the total number of complaints received for causes such as infection.

Your firm's complaint log containing 15,880 complaints received between 7/1/2014 and 9/9/2016 indicates that the most commonly used Complaint Category is "Medical: Revision due to Infection" (1,257 complaints). Two other categories referencing infection have also been used: "Medical: Infection" (180 complaints) and "Functional: Revision due to infection" (53 complaints).

An additional 804 complaints include the word "infection" in the Complaint Description field but indicate Complaint Categories other than the three listed above. We reviewed 11 of these 804 complaints with your Post Market Surveillance Manager, who confirmed that 4 of the 11 should have been assigned an infection-related Complaint Category.

Observation 8A Investigation and Response:

On December 1, 2016, Zimmer Biomet opened CAPA CA-03085 to investigate the root causes of, and to determine and implement effective corrective actions to prevent recurrence of, the issues regarding coding of complaints identified in Observation 8A (see attachment 8A-A, *CAPA CA-03085*). CAPA CA-03085 is currently in the Investigation Phase.

Although complete root cause analysis is still underway, Zimmer Biomet's preliminary review indicates that, in addition to the finding in the Observation (b) (4) ((b) (4)), (b) (4) team members

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were coding complaints in (b) (4) by using (b) (4)
(b) (4)
(b) (4)
described below.

During the inspection on November 14, 2016, Zimmer Biomet implemented interim control IC-016 to govern complaint handling at the Warsaw North Campus (see attachments 8A-B, *IC-016 Revision 1,* (b) (4) *for IC-016 Rev 1*. IC-016 includes a Reporting Guidance Document ("RGD") that provides standardized code definitions for complaint handlers (see attachment 8A-M, (b) (4)). (b) (4)
he RGD lists the Complaint Categories to be used and an associated definition and summary of failure for each. The complaints reviewed by the Investigators during the inspection were opened prior to the implementation of clear code definitions on November 14, 2016. Additionally, the RGD includes Medical Device Report ("MDR") patient and device codes to ensure consistent coding for Complaint Categories. Warsaw North Campus will continue to operate under IC-016 and its RGD until Zimmer Biomet identifies and implements appropriate systemic corrective actions including, but not limited to, updates to relevant procedures.

As an immediate containment action to address the Observation's finding regarding coding of complaints related to infection and to determine whether any new safety signals require action, the (b) (4) team analyzed complaint data for all complaints containing codes for or narrative references to infection. (b) (4)

Although Zimmer Biomet intends to undertake a comprehensive (b) (4) review and remediation of Complaint Category codes, as described below, Zimmer Biomet has already reviewed the Complaint Category coding in the eleven complaint files that the Investigators reviewed during the inspection and that form the basis of Observation 8(A). Zimmer Biomet determined that (b) (4)
During this initial review, Zimmer Biomet determined that (b) (4)
consistent with the code definitions implemented under IC-016. Zimmer Biomet updated the Complaint Category codes for complaint numbers CMP-0212756, CMP-0200344, CMP-0225049, CMP-0200016, CMP-0198311, and CMP-0159160. Additionally, the review determined (b) (4) -

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(b) (4)

Under the investigation plan for CAPA CA-03085, Zimmer Biomet performed a quality record search analysis ("QRSA") to identify any other CAPA or audit findings related to complaint coding (see attachment 8A-L, (b) (4)). The QRSA determined that (b) (4) Observation 8(A), were found within Zimmer Biomet North. As an investigation action, Zimmer Biomet will also determine the requirements for updating (b) (4) to permit coding of multiple values in the Complaint Category field, by determining whether: (b) (4) . Following these investigation steps, Zimmer Biomet will update (b) (4) to permit the selection of multiple Complaint Category codes; details and a timeline for this action will be provided in future updates to this response. Finally, Zimmer Biomet will reassess the RGD prior to undertaking a (b) (4) .

Zimmer Biomet intends to conduct a (b) (4) review and (b) (4) of all (b) (4) complaints received in the (b) (4) prior to the implementation of IC-016 and the RGD, (b) (4) . The (b) (4) review and (b) (4) will be conducted under a protocol to be developed following the completion of the CAPA investigation regarding the complaint coding issues identified in Observation 8(A). If any changes to complaint coding as a result of the (b) (4) review and (b) (4) , Zimmer Biomet will file MDRs as needed. Zimmer Biomet will develop the protocol and timeline for completion before the CAPA enters the Implementation Phase and will provide information regarding the development of these activities in future updates. (b) (4) Future updates to this initial response will contain

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timelines and information regarding these actions, when the CAPA moves to the Implementation Phase.

Completed Actions:

No.	Action	Completion Date
8A-1	Implemented Interim Control IC-016 to govern all complaint handling at Warsaw North Campus (see attachment 8A-B) which contained the Reporting Guidance Document (RGD) , Revision 1 to provide coding guidance, define Complaint Category codes, summarize failures, and identify MDR patient and device codes.	November 14, 2016
8A-2	Released Reporting Guidance Document (RGD), Revision 2, as it's own document, (see attachment 8A-M).	December 13, 2016
8A-3	Conducted (b) (4) using data from all complaints containing codes or narrative references to infection for the last (b) (4) (b) (4) (see attachments 8A-C).	December 14, 2016
8A-4	Initiated CAPA CA-03085 to address the issues identified in Observation 8(A) (see attachment 8A-A).	December 1, 2016
8A-5	CMP-0212756: • Updated complaint file with Complaint Category of "Medical: Revision due to infection" (see attachment 8A-D). • Reassessed complaint for reportability.	December 5, 2016
8A-6	CMP-0200344: • Updated complaint file with Complaint Category of "Medical: Revision due to infection" (see attachment 8A-E). • Reassessed complaint for reportability.	December 5, 2016
8A-7	CMP-0225049: • Updated complaint file with Complaint Category of "Medical: Revision due to infection" (see attachment 8A-F). • Reassessed complaint for reportability.	December 5, 2016
8A-8	CMP-0200016: • Updated complaint file with Complaint Category of "Medical: Revision due to infection" (see attachment 8A-G). • Reassessed complaint for reportability.	December 5, 2016
8A-9	CMP-0198311: • Updated complaint file with Complaint Category of "Medical: Revision due to infection" (see attachment 8A-H). • Reassessed complaint for reportability.	December 5, 2016
8A-10	CMP-0159160: • Updated complaint file with Complaint Category of "Medical:	December 5, 2016

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	Revision due to infection" (see attachment 8A-I). • Reassessed complaint for reportability.	
8A-11	CMP-0174209: • Updated complaint file with Complaint Category of "Medical: Revision due to infection" (see attachment 8A-J). • Reassessed complaint for reportability.	December 5, 2016
8A-12	Performed quality record search analysis (QRSA) to identify other CAPA or Audit findings related to complaint coding (see attachment 8A-L).	December 8, 2016

Planned Actions:

No.	Action	Completion Date
8A-13	Complete Root Cause/Action Plan Phase, root cause determination and identification of corrective actions under CAPA CA-03085. • Determine requirements for updating (b) (4) (b) (4) • Define improvements to complaint coding process.	(b) (4)
8A-14	Complete CAPA CA-03085 Action Implementation Phase. • (b) (4) • Update (b) (4) to (b) (4) • Release revised Complaint Handling procedures.	Target completion date to be reported in a future update
8A-15	Verify effectiveness of CAPA CA-03085 and close CAPA.	Target completion date to be reported in a future update

B. Your firm's Product Complaint Procedure, SOP 14.0.1 Rev. 20, is inadequate in that Device History Record (DHR) reviews performed during complaint investigations do not consistently identify/document activities that could potentially contribute to the occurrence of a complaint event.

During interviews with three Quality Engineers who are responsible for investigating complaints, we provided three DHRs for Oxford Knee tibial tray components (part number 154727, lot numbers M319970, M320070, and M394040) indicating that all devices were rejected at final inspection (inspection step 0160) one or more times before being accepted on 9/6/2016, 9/8/2016, and 9/13/2016. When asked how they would document

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the results of the DHR reviews, the Quality Engineers stated they would document "no anomalies found" because no devices were documented as scrapped and no *Product Deviation/Reject Reports (i.e.,* nonconforming product records) were documented *for* these lots.

Observation 8B Investigation and Response:

On December 1, 2016, Zimmer Biomet opened CAPA CA-03094 to investigate and address the finding in Observation 8(B) that Device History Record ("DHR") reviews performed during complaint investigations do not consistently identify and document activities that could potentially contribute to the occurrence of a complaint event (see attachment 8B-A, *CAPA CA-03094 Summary*). CAPA CA-03094 is currently in the Investigation Phase.

During the recent inspection, FDA Investigators interviewed three Quality Engineers that conduct complaint investigations at the Warsaw North Campus. (b) (4)

.

(b) (4)

As described in the response to Observation 8(A), during the inspection and following the hypothetical complaint investigation that resulted in the findings in Observation 8(B), Zimmer Biomet implemented Interim Control IC-016, on November 14, 2016 to govern the complaint handling process at Warsaw North Campus (see attachment 8A-B, *IC-016* Interim Control for

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(b) (4) *for IC-016 Rev 1*. IC-016 revises the previous Warsaw North Campus process for DHR review and documentation. It requires the review of DHRs relevant to a complaint for any information that may be related to the reported failure, including scrap, NCRs, deviations, and sterility certifications. Under IC-016, the (b) (4) must summarize this DHR review in the complaint file, including any deviations or other anomalies identified. (b) (4) .

To investigate the finding in Observation 8(B) and to appropriately identify and scope corrective actions, Zimmer Biomet conducted a quality record search analysis ("QRSA") to determine if there are existing quality records or CAPAs related to this issue (see attachment 8B-B, (b) (4) (b) (4)). Zimmer Biomet also reviewed a sample of DHR reviews documented in complaint files in the (b) (4) to determine whether there were any gaps in the DHR record or deviation report review portion of the sampled complaint records and, if so, whether the gaps impacted safety signal identification (see attachment 8B-C, *DHR Review Results & Summary*). This review found that (b) (4)

and current (b) (4) Phase of CAPA (b) (4) .

Please note that in addition to the activities being conducted under CAPA CA-03094 to address the DHR review process and documentation during complaint investigations, two additional CAPAs are currently active at Warsaw North Campus to address topics that concern topics related to the finding in Observation 8(B): CAPA CA-02645 and CAPA CA-02623. CAPA CA-02645 concerns the non-conformance process and is discussed in Observations 3(A), 3(B), 3(C), and 12. CA-02623 concerns documentation practices for DHRs and pre-dates the recent FDA inspection.

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Completed Actions:

No.	Action	Completion Date
8B-1	Implemented Interim Control IC-016 to revise the process for conducting and documenting DHR reviews during complaint investigation (see attachment 8A-B).	November 14, 2016
8B-2	Initiated CAPA CA-03094 to address the issues identified in Observation 8(B) (see attachment 8B-A).	December 1, 2016
8B-3	Conducted review of sample of DHR reviews in complaint files opened (b) (4) to understand the impact of gaps in the DHR record/deviation report when conducting the DHR review portion of a complaint investigation and ensure no impact safety signal identification (see attachment 8B-C).	December 15, 2016
8B-4	Performed quality record search analysis to identify existing quality records or CAPAs related to the finding in Observation 8(B) (see attachment 8B-B).	December 13, 2016

Planned Actions:

No.	Action	Completion Date
8B-5	Complete Root Cause/Action Plan Phase, root cause determination and identification of corrective actions under CAPA CA-03094. • Investigate best practices for DHR reviews and perform gap analysis of IC-016 and current procedures to best practices.	February 3, 2017
8B-6	Complete CAPA CA-03094 Action Implementation Phase. • Update IC-016 with DHR review improvements • Release harmonized procedure	Target completion date to be reported in a future update
8B-7	Verify effectiveness of CAPA CA-03094 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #9(A)

Procedures for acceptance activities have not been adequately established.

Specifically,

A. Procedures for verifying the thickness of (b) (4) porous coatings have not been adequately established. According to your firm's *Health Hazard Evaluation Determination #09-2016-095* (initiated 9/26/2016) the coating (b) (4)

Process Engineering Specification 1.1: **(b) (4) (Rev. 58, effective 6/20/2016) requires that devices (b) (4) However, on 09/12/2016, we observed an operator verify the overall dimensions of a Taperloc femoral hip implant (item number 11-103208, lot number M525020) *after it had been coated.* Dimensional measurements taken prior to porous coating are not documented. As such, your firm could not provide objective evidence that the porous coat thickness specified by *Process Engineering Specification 1.1* has been met.**

Notably, the worst-case tolerance stack-up condition between the coating thickness and the dimension(s) of the substrate allows for the possibility that devices with a porous coating thickness below the minimum specification are not identified as nonconforming product during inspection. For example, a tolerance stack-up analysis performed by your firm during this inspection of a Taperloc femoral hip implant indicated a worst-case coating thickness of (b) (4) inches that would pass final inspection. This worst-case thickness is (b) (4) % less than the minimum specification of (b) (4) inches defined by *Process Engineering Specification 1.1.*

Dimensional measurements taken prior to porous coating are also not documented for at least 5 of 7 other (b) (4) devices reviewed during this inspection. Specifically:

Finished Item Number	Device Description
192110	Echo Porous Lateral Femoral Hip Stem

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113626	**Comprehensive Primary Mini Shoulder Stem**
11-301325	**Arcos Standard Hip Stem**
150464	**OSS Diaphyseal Segment**
113604	**Comprehensive Primary Micro Shoulder Stem**

Observation 9(A) Investigation and Response:

During the recent inspection, on September 19, 2016, Zimmer Biomet initiated CAPA CA-02865 to address procedures for verifying the thickness of (b) (4) coatings on products manufactured at the Warsaw North Campus as identified in Observation 9(A) (see attachment 9A-A, *CAPA CA-02865 Summary*). CAPA CA-02865 is currently in the Investigation (Root Cause/Action Plan) phase. In addition, Zimmer Biomet has initiated CAPA CA-02894 to address system-wide issues concerning acceptance activities at Zimmer Biomet's Warsaw North Campus. CA-02894 is discussed further in the response to Observation 9(B).

Prior to the inspection, to measure the thickness of (b) (4) coatings, Zimmer Biomet measured the (b) (4) (b) (4) . (b) (4) of the (b) (4) (b) (4) was performed; (b) (4) .

Zimmer Biomet has taken the following containment actions to address the issues related to (b) (4) coating thickness identified in Observation 9(A):

- [redacted]

Additionally, as an immediate correction, on October 21, 2016, Zimmer Biomet began documenting (b) (4) data to verify thickness. As for December 15, 2016, the following process has been formally implemented for verifying thickness on all (b) (4) coated products produced at the Warsaw North Campus:

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- (b) (4) are measured and measurements are recorded on a Manufacturing Process Form *MPF 0107* (see attachment 9A-D, *MPF 0107*) prior to the application of the (b) (4) coating, per inspection criteria *I00117* (b) (4) (see attachment 9A-E, *I00117* (b) (4)).
- Post-spray dimensions are recorded on *MPF 0107* in order to determine the thickness of the coating.
- The dimensional data recorded on *MPF 0107* is stored in the (b) (4) for objective evidence that the thickness requirement has been met on 100 percent of parts produced.

Zimmer Biomet also took action to evaluate the potential product impact if the thickness of the Taperloc product (b) (4) coating is less than (b) (4) inches. On September 26, 2016, Zimmer Biomet initiated a Health Hazard Evaluation Determination ("HHED") to consider whether a Health Hazard Evaluation ("HHE") was needed to evaluate the impact of Taperloc products' (b) (4) coating thickness (see attachment 9A-F, *HHED 09-2016-095*). The HHED concluded that an HHE was needed and, accordingly, an HHE was initiated and executed. (b) (4) The HHE evaluated that the possibility of a (b) (4) spray coating and determined that (b) (4)

Additional HHEs were completed for the remaining product families referenced in Observation 9(A), as follows:

Device Description	**Finished Item Number**	**Health Hazard Evaluation**	**Date**	**HHE result**
Echo Porous Lateral Femoral Hip Stem	(b) (4)	HHE 2016-300 (see attachment 9A-H, *HHE 2016-300*)	December 16, 2016	(b) (4)
Comprehensive Primary Mini Shoulder Stem	(b) (4)	HHE 2016-308 (see attachment 9A-I, *HHE 2016-308*)	December 16, 2016	(b) (4)
Arcos Standard Hip Stem	(b) (4)	HHE 2016-300 (see attachment 9A-H, *HHE 2016-300*)	December 16, 2016	(b) (4)

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OSS Diaphyseal Segment	(b) (4)	HHED 12-2016-031 (see attachment 9A-J, *HHED 12-2016-031*)	December 19, 2016	(b) (4)
Comprehensive Primary Micro Shoulder Stem	(b) (4)	HHE 2016-308 (see attachment 9A-I, *HHE 2016-308*)	December 16, 2016	(b) (4)

In the case of each product in the table above, significant external clinical data was available and evaluated. Each HHE evaluated (b) (4) . Based on long-term clinical success for the (b) (4) products produced at the Warsaw North Campus, Zimmer Biomet's (b) (4) reviewed the HHEs and determined that (b) (4)

Zimmer Biomet will continue the CAPA CA-02865 investigation, which includes the following tasks:

1. Conduct formal root cause analysis for issues identified in Observation 9(A);
2. Conduct investigation into test methods associated with the (b) (4) operation;
3. Develop implementation plan for CAPA CA-02865; and
4. Develop verification of effectiveness ("VoE") plan for CAPA CA-02865.

Zimmer Biomet is committed to providing additional information on the progress of the CAPA investigation in regular updates to FDA.

Completed Actions:

No.	Action	Completion Date
9A-1	Initiated CAPA CA-02865 to address issues identified in Observation 9(A) (see attachment 9A-A).	September 19, 2016
9A-2	Initiated an HHED for the Taperloc product which concluded that HHE was needed (see attachment 9A-F).	September 26, 2016
9A-3	(b) (4)	October 3, 2016
9A-4	(b) (4)	October 3, 2016
9A-5	(b) (4)	October 3, 2016
9A-6	Instituted 100 percent thickness verification on all (b) (4) products	October 21, 2016

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	produced at the Warsaw North Campus by recording measurements on *MPF 0107* (see attachment 9A-D).	
9A-7	Completed *HHE 2016-241* for the (b) (4)	December 16, 2016
9A-8	Completed revision of inspection criteria *I00117* (b) (4) (b) (4) (see attachment 9A-E).	December 16, 2016
9A-9	Completed *HHE 2016-300* for Echo Porous Lateral Femoral Hip Stem product (see attachment 9A-H).	December 16, 2016
9A-10	Completed *HHE 2016-308* for Comprehensive Primary Mini Shoulder Stem (see attachment 9A-I).	December 16, 2016
9A-11	Completed *HHE 2016-300* for Arcos Standard Hip Stem (see attachment 9A-H).	December 16, 2016
9A-12	Completed *HHED 12-2016-031* for OSS Diaphyseal Segment (see attachment 9A-J).	December 19, 2016
9A-13	Completed *HHE 2016-308* for Comprehensive Primary Micro Shoulder Stem (see attachment 9A-I).	December 16, 2016

Planned Actions:

No.	Action	Completion Date
9A-14	Conduct formal root cause analysis for issues identified in Observation 9(A).	(b) (4)
9A-15	Conduct investigation into test methods associated with the (b) (4) (b) (4) for thickness.	(b) (4)
9A-16	Conduct investigation of all CTQ features associated with the (b) (4) .	(b) (4)
9A-17	Complete Root Cause/Action Plan Phase for CAPA CA-02865.	Target completion date to be reported in a future update
9A-18	Complete Implementation Phase for CAPA CA-02865.	Target completion date to be reported in a future update
9A-19	Verify effectiveness of CAPA CA-02865 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #9(B)

B. Acceptance records do not include the equipment used. In 35 of 35 DHRs sampled, not all equipment used during acceptance activities were documented. Each DHR references inspection criteria equipment that must be used, but the actual gage numbers used to perform inspections are routinely not documented. For example:

Number of DHRs	Device	Inspection Criteria Document	Manufacturing Step	Inspected Feature	Equipment Required
5 of 35	ArCom XL Liner (item number XL - 105923)	i03523 (Rev 26, 11/15/2012)	(b) (4)	"Outside lip diameter"	(b) (4)
				"100% distance across tab radii"	(b) (4) "
5 of 35	Vanguard PS femoral knee implant (item number 183228)	i07612 (Rev 13, 05/04/2016)	(b) (4)	"Intercondylar box wall thickness"	(b) (4)
				"100% location of PS cam from inside of distal condyle"	(b) (4)
5 of 35	Oxford knee tibial tray (item number 154727)	i11427 (Rev 4, 09/12/2013)	(b) (4)	"100% Rail thickness"	(b) (4)
				"100% Bearing surface"	(b) (4)
				"100% bottom thickness"	(b) (4)
				"100% Radius at back corner of rail"	(b) (4)

Your firm's Quality Director confirmed that operators utilize (b) (4) piece of equipment (uniquely identified by (b) (4)) for each type of equipment shown in this column. A memo provided by the firm explained that when a caliper, micrometer, indicator, radius gage, or ball micrometer is required by the Inspection Criteria, the inspection criteria are referencing a "standard use" version of the gage. The inspection criteria could refer to any of (b) (4) standard use 0-6" calipers, (b) (4)

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standard use 0-1' micrometers, (b) (4) standard use 0-2' Indicators, (b) (4) standard use radius gage sets and (b) (4) ball micrometers.

Your firm was unable to provide documented justification for why actual equipment used was not documented in each of the 35 DHRs (11/18/2016).

Observation 9(B) Investigation and Response:

During the recent inspection, on September 25, 2016, Zimmer Biomet initiated CAPA CA-02894 to address the issues identified in Observation 9(B) (see attachment, 9B-A, *CAPA CA-02894 Summary*). As noted in Observation 9(B), although device history records ("DHRs") at Zimmer Biomet's Warsaw North Campus reference equipment that must be used to perform inspections, it appears that the actual equipment gage numbers used to perform inspections routinely are not documented.

Earlier this year, Zimmer Biomet (b) (4) Accordingly, on June 20, 2016, Zimmer Biomet initiated CAPA CA-02623 to address DHR completeness and correctness. CAPA CA-02623 is further addressed in Discussion Point 5

CAPA CA-02894 currently is in the investigation (Root Cause/Action Plan) phase.

After the issue was raised during the inspection, Zimmer Biomet made several corrections to its documentation of acceptance activities. Specifically, Zimmer Biomet completed the following correction/containment activities:

- On October 4, 2016, created form MPF0107 (see attachment 9B-B, *MFP0107* (b) (4)), which lists equipment gage numbers and the following information:
  - (b) (4)

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Since its implementation on October 4, 2016, Zimmer Biomet has updated MPF0107 twice, on October 20, 2016, and on November 11, 2016. Both updates were intended to clarify the form (see attachment 9B-C, *MPF0107 Rev. 2*, and attachment 9B-D, *MPF0107 Rev. 3*).

- On October 27, 2016, updated work instruction WI00153 (see attachment 9B-E, *WI00153* (b) (4) *Rev.4*), which provides instructions for completing form MPF0107. Zimmer Biomet has updated WI00153 twice, on November 11, 2016, and November 23, 2016. Both updates were minor and were intended to help clarify MPF0107 (see attachment 9B-F, *WI00153 Rev. 5*, and attachment 9B-G, *WI00153 Rev. 6*).

- On (b) (4), completed training of all relevant processing team members, including team members conducting final inspections, for filling out necessary data collection requirements in compliance with the newly revised process. Team members conducting final inspections will assess the information on form MPF0107 and verify that inspection equipment meets criteria requirements and is within specification (see attachment 9B-H, *Training to MPF0107 and WI00153*). (b) (4)

- On October 8, 2016, created form MPF0109 to guide team members conducting final inspections (see attachment 9B-I, *MPF0109* (b) (4)). On October 20, 2016, Zimmer Biomet updated the form to provide further clarity (see attachment 9B-J MPF0109 Rev. 2).

- On October 19, 2016, created work instruction WIG0233 (see attachment 9B-K, *WIG0233 Device History Record (DHR) Review*), which identifies the elements in each production order that must be reviewed and recorded on form MPF0109.

- On (b) (4), completed training of all team members conducting final inspections on MPF0109 and WIG0233 for review of the DHR at final inspection (see attachment 9B-L, *Training to MPF0109 and WIG0233*).

Pursuant to CAPA CA-02894, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 9(B);

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2. Review a sample of DHRs from the Warsaw North Campus to evaluate their compliance with 21 C.F.R. § 820.80(e). Any data or trends that indicate a potential impact to product or patient safety shall be accessed through our HHED process as applicable. ;
3. Develop an implementation plan and verification of effectiveness ("VoE") plan to address root causes;
4. Search quality records for past CAPAs and issue evaluations ("IEs") for similar issues; and

Completed Actions:

No.	Action	Completion Date
9B-1	Initiated CAPA CA-02894 to address the issues identified in Observation 9(B) (see attachment, 9B-A,).	September 25, 2016
9B-2	Created form MPF0107 (see attachment 9B-B, *MPF0107* (b) (4)). Initial version was implemented on October 4, 2016, with subsequent revisions being implemented on October 20, 2016 (attachment 9B-C), and November 11, 2016 (attachment 9B-D).	October 4, 2016
9B-3	Created form MPF0109 (see attachment 9B-I, *MPF0109* (b) (4)). The initial form was implemented on October 8, 2016, with the subsequent form being implemented on October 20, 2016 (attachment 9B-J)	October 8, 2016,
9B-4	Created work instruction WIG0233 (see attachment 9B-K).	October 19, 2016
9B-5	Completed training of all team members conducting final inspections on MPF0109 and WIG0233 for review of the DHR at final inspection (see attachment 9B-L).	October 21-25, 2016
9B-6	Updated work instruction WI00153 (see attachment 9B-E, *WI00153* (b) (4)). The initial update was implemented on October 27, 2016, with subsequent revisions implemented on November 11, 2016 (attachment 9B-F) and November 23, 2016 (attachment 9B-G).	October 27, 2016
9B-7	Completed training of all relevant processing team members on form MPF0107 and work instruction WI00153 (see attachment 9B-H).	November 8-11, 2016

Planned Actions:

No.	Action	Completion Date
9B-8	Conduct a root-cause analysis of the issues identified in Observation 9(B).	(b) (4)
9B-9	Review a sample of DHRs from the Warsaw North Campus to evaluate their compliance with 21 C.F.R. § 820.80(e).	(b) (4)

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9B-10	Search quality records for past CAPAs and IEs for similar issues.	(b) (4)
9B-11	Complete CAPA CA-02894Root Cause/Action Phase.	
9B-12	Complete CAPA CA-02894 implementation phase.	Target completion date to be reported in a future update
9B-13	Verify effectiveness of CAPA CA-02894 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #10

Buildings are not of suitable design to perform necessary operations.

Specifically,

Your firm's gowning areas and work environments (WE) are not consistently designed and constructed in a manner that ensures in-process devices will be protected from personnel and conditions that may adversely impact product quality. For example:

A. **Your firm's Work Environment Room Rules, Gowning and Ungowning Procedure, INST 9.5.8.12 Rev. 1 effective 08/29/2016, requires gowning to be completed prior to entering work environments. However, the layouts for your firm's (b) (4) require personnel to enter and/or pass thru the WE before gowning can occur.**

B. **Your firm's (b) (4) is not physically segregated from common areas where ungowned personnel travel. The (b) (4) contains a walkway along the east wall of the room that is only segregated from the rest of the room by a line of tape along the floor. While observing operations in the (b) (4) we noted personnel in street clothing traversing this walkway to access the (b) (4) Cleanroom Gowning Area (b) (4) and passing within one (1) foot of work benches on which final inspection of (b) (4) was occurring. Furthermore, (b) (4) personnel must cross into this walkway to:**

   i. **Place totes containing in-process and finished devices onto storage racks.**

   ii. **Transfer totes via pass-thru from the (b) (4) to the (b) (4) Cleanroom ((b) (4)**

Observation 10 Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated CAPA CA-03086 to address the issues identified in Observation 10 (see attachment 10-A, *CAPA CA-03086 Summary*). CAPA CA-03086 is currently in the Investigation (Root Cause/Action Plan) Phase.

Observation 10 concerns gowning areas and work environments at Zimmer Biomet's Warsaw North Campus. At Zimmer Biomet, a work environment is "(b) (4)

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(b) (4)

During the recent inspection, Zimmer Biomet (b) (4) that could be affected by the issues identified in Observation 10. During the inspection, Zimmer Biomet (b) (4) at the (b) (4) Warsaw North Campus in response to the FDA Investigators; findings. (b) (4)

(b) (4)

.

(b) (4)

, Zimmer Biomet implemented (b) (4)

Finally, with regard (b) (4) Zimmer Biomet completed a health hazard evaluation determination ("HHED") (see attachment 10-E HHED# 12-2016-007 and HHED # 12-2016-034) to determine the risks associated with the gowning area and work environment issues and the actions, if any, Zimmer Biomet should take to resolve them. The determination reached in HHED 12-2016-007 and HHED 12-2016-034 was that (b) (4)

.

Zimmer Biomet will provide details regarding any decisions reached or actions taken as a result of the HHE in our update on January 17, 2017.

During the recent inspection, Zimmer Biomet's (b) (4) toured the Warsaw North Campus to review environmental controls. The team recommended several improvements related to gowning practices, cleanroom behavior, and material transfer between different classified areas, and implementation of the recommendations began immediately, as set forth in the following table:

Table. Implementation of Recommendations:

Objective evidence	Number of document or location of evidence	Date of completion
In-house training—Sanitization methods	Training records on file	October 17, 2016
In-house training—Introduction to microbiology	Training records on file	October 10-11, 2016

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and cleanroom behavior		
HEPA certifications—Certification of HEPA filters in cleanrooms and work environments (see attachment 10-F)	IC 006	October 21, 2016
Cleanroom compatible equipment to be used in work environments—(b) (4)	Purchasing documents on file	Installed during October 2016
Work environment drawings (b) (4) (see attachment 10-G)	INST 9.5.9.10 INST 9.5.9.12 INST 9.5.9.13 INST 9.5.9.14 INST 9.5.9.15 INST 9.5.9.19	November 15, 2016 November 15, 2016 November 15, 2016 November 11, 2016 November 15, 2016 November 15, 2016
Documented update for cleanroom/work environment practices—(b) (4) (see attachments 10-B and 10-H)	IC 007 IC 024	October 31, 2016

During the inspection, Zimmer Biomet implemented an interim control intended to describe the routine operating procedures for environmentally controlled areas, including gowning procedures and personnel flow (see attachment 10-H, *IC 024 Environmentally Controlled Areas: Cleanroom and Work Environment Practices*). Additionally, Zimmer Biomet conducted in-house training on *IC 024 Environmentally Controlled Areas*: Cleanroom and Work Environment Practices (see attachment 10-I).

Pursuant to CAPA CA-03086, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 10 for each work environment at the Warsaw North Campus;
2. Review the process of storing in-process and finished product locations;
3. Review the transfer of product (b) (4) from the work environment to cleanroom process and determine appropriate procedure;
4. Perform a walkthrough of Warsaw Campus North gowning areas and work environments to determine if the areas are adequate for their intended use;

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5. Perform a walkthrough of Warsaw Campus North gowning areas and work environments to determine if the design and layout are appropriate for their intended use; and
6. Based on root causes, develop implementation and verification of effectiveness ("VoE") plans.

Completed Actions:

No.	Action	Completion Date
10-1	Toured the Warsaw North Campus and reviewed environmental controls; recommended several improvements related to gowning practices, cleanroom behavior, and material transfer between different classified areas; and began implementing the recommendations.	September 19, 2016
10-2	(b) (4)	September 29, 2016
10-3	(b) (4)	September 29, 2016
10-4	Initiated CAPA CA-03086 to address the issues identified in Observation 10 (see attachment 10-A).	December 1, 2016
10-5	Released Interim Control IC 024 intended to describe the routine operating procedures for environmentally controlled areas, including gowning procedures and personnel flow (see attachment 10-H).	December 16, 2016
10-6	Conducted in-house training on IC 024 Environmentally Controlled Areas: Cleanroom and Work Environment Practices (see attachment 10-I)	December 19, 2016
10-7	Completed HHED 12-2016-007 and HHED 12-2016-034 (see attachment 10-E) that concluded (b) (4)	December 16, 2016

Planned Actions:

No.	Action	Completion Date
10-8	Complete HHE 2016-311 to determine the risks associated with gowning area and work environment issues and the actions, if any, Zimmer Biomet should take to resolve them.	(b) (4)
10-9	Conduct a root-cause analysis of the issues identified in Observation 10 for work environments at the Warsaw North Campus.	(b) (4)
10-10	Review the process of storing in-process and finished product (b) (4)	(b) (4)

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	(b) (4) locations.	
10-11	Review the transfer of product (b) (4) from the work environment to cleanroom process and determine appropriate procedure.	(b) (4)
10-12	Perform a walkthrough of the Warsaw Campus North gowning areas and work environments to determine if the areas are adequate for their intended use.	(b) (4)
10-13	Perform a walkthrough of the Warsaw Campus North gowning areas and work environments to determine if the design and layout are appropriate for their intended use.	(b) (4)
10-14	Complete CAPA CA-03086 Root Cause/Action Plan Phase.	(b) (4)
10-15	Complete CAPA CA-03086 Implementation Phase.	Target completion date to be reported in a future update
10-16	Implement the use of (b) (4) hoods for final upgrade/bioburden reduction.	(b) (4)
10-17	Install additional HEPA filters in classified areas and work environments where applicable.	(b) (4)
10-18	Verify effectiveness of CAPA CA-03086 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation 11

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FDA Observation #11

Sampling plans are not based on valid statistical rationale.

Observation 11 Investigation and Response:

On December 1, 2016, Zimmer Biomet initiated two CAPAs that address, in part, system-wide issues concerning the use of statistical rationales to define sampling plans. CAPA CA-03083 was opened to address process monitoring Observations 7(A) and 7(B), including the finding regarding statistical rationales for sampling plans in process monitoring activities, documented in Observation 7(A). CAPA CA-03083 is discussed further in the responses to Observations 7(A) and 7(B). CAPA CA-03082 was opened to address findings regarding statistical rationales for sampling plans, including the finding regarding sampling plans for in-process inspections and final release inspections and testing for LactoSorb product, documented in Observations 11(A) and (B) (see attachment 11-A, *CAPA CA-03082 Summary*).

These two CAPAs will run in parallel and, through the combined efforts under these CAPAs, ensure that Zimmer Biomet will evaluate all procedures, forms, and work instructions associated with statistical rationales for sampling plans at the Warsaw North Campus to ensure that the quality system is compliant with the requirements of 21 C.F.R. § 820.250. Specifically, Zimmer Biomet will ensure that procedures, forms, and work instructions address:

1. Identification, use, and documentation of a valid statistical rationale to support sampling plans for:

    a. Process monitoring;
    b. In-process inspections;
    c. Final release inspections/testing;
    d. Any other processes at the Warsaw North Campus that employ sampling plans; and

2. Establishment and maintenance of procedures that ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed and documented.

Zimmer Biomet will revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of each of the foregoing quality system requirements. Specific revisions will be identified following the completion of the Investigation Phase of CAPAs CA-03083 and CA-

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03082, which will include: (1) completion of a root cause analysis and (2) identification of sampling plans in use at the Warsaw North Campus that lack documentation of a statistical rationale. In addition to (b) (4), as needed, to existing procedures, forms, and work instructions, the (b) (4)

Zimmer Biomet will provide details regarding actions identified as a result of the investigation conducted under CAPAs CA-03083 and CA-03082 in future updates to responses associated with Observation 7(A)/7(B) and Observation 11(A)/11(B) respectively.

In addition to these system-wide actions, Zimmer Biomet will take specific actions to identify and implement appropriate corrections and corrective actions to address the findings regarding sampling plans for inspections of LactoSorb products identified in Observations 11(A) and 11(B); those specific actions are discussed in further detail in the applicable sub-sections of this response.

Completed Actions:

No.	Action	Completion Date
11-1	Initiated CAPA CA-03082 to address the issues identified in Observations 11(A) and 11(B) with respect to statistical rationale for sampling plans (see attachment 11-A).	December 1, 2016

Planned Actions:

No.	Action	Completion Date
11-2	Conduct root cause analysis for CAPA CA-03082 to determine why sampling plans identified Observation 11(A) and 11(B) were (b) (4)	(b) (4)
11-3	Under CAPA CA-03082, identify all procedures that define sampling plans for inspection/release testing used at Warsaw North Campus and determine if sufficient statistical rationale is available for each.	(b) (4)
11-4	Under CAPA CA-03082, determine if any additional containment actions are required following completion of root cause analysis for inspections/release testing with insufficient statistical rationales.	(b) (4)
11-5	Under CAPA CA-03082, identify sampling plans in use at the Warsaw North Campus for inspections/release testing that lack documentation of a sufficient statistical rationale.	(b) (4)
11-6	Conduct root cause analysis for CAPA CA-03082 to determine why sampling plans identified in action 11-5 were (b) (4) .	(b) (4)

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11-7	Complete CAPA CA-03082 Root Cause/Action Plan Phase.	(b) (4)
11-8	Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of statistical rationales for sampling plans.	Target completion date to be reported in a future update
11-9	Complete CAPA CA-03082 Action Implementation Phase.	Target completion date to be reported in a future update
11-10	Verify effectiveness of CAPA CA-03082 and close CAPA.	Target completion date to be reported in a future update

FDA Observation #11(A)

Specifically,

A. Sampling plans used for inspections/release testing are not consistently based on a valid statistical rationale in accordance with QM 20.0 Statistical Techniques procedure, Rev. 8 effective 09/19/2011. For example, according to QP0010 Inherent Viscosity Testing for LactoSorb, Version 11 effective 05/03/2012:

i. Finished LactoSorb plates made from (b) (4) require (b) (4) sample/mfg lot after sterilization. Review of the five largest screw DHRs revealed manufactured quantities between (b) (4) (b) (4) devices per lot. Your firm has distributed at least (b) (4) Lactosorb plate devices from (b) (4) .

ii. Finished LactoSorb screws made from (b) (4) require (b) (sample/mfg lot after sterilization. Review of the five largest screw DHRs revealed all five lots contained (b) (4) devices. Your firm has distributed at least (b) (4) Lactosorb devices that have been manufactured from (b) (4) from (b) (4) (b) (4) .

Observation 11(A) Investigation and Response:

As explained in the response to Observation 11 above, on December 1, 2016, Zimmer Biomet initiated CAPA CA-03082 to address the issues identified in the FDA-483 concerning the statistical rationale for sampling plans in use at the Warsaw North Campus (see attachment 11-A, *CAPA CA-03082 Summary*). CAPA CA-03082 is currently in the Investigation Phase. In addition to addressing system-wide corrective actions regarding statistical rationales for sampling plans, CAPA CA-03082 also addresses the specific findings in Observations 11(A) and

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11(B) regarding the statistical rationale for sampling plans for lot acceptance for LactoSorb products.

As an (b) (4) during the recent inspection, Zimmer Biomet (b) (4) production (b) (4), during the inspection (b) (4) are established to address all observations associated with the (b) (4) process. Additionally, Zimmer Biomet (b) (4) controlled by Zimmer Biomet: (b) (4) following (b) (4) sterilization and due to findings regarding the validation of the LactoSorb cleaning process, as identified in Observation 1(H).

In addition, as a correction, Zimmer Biomet conducted a study of the inherent viscosity testing for LactoSorb products, as currently conducted under QP0010, (b) (4), Rev. 11. The study reviewed the testing of (b) (4) per lot, after sterilization, of finished LactoSorb plates (b) (4) and of finished LactoSorb screws made from (b) (4), as identified in the examples in Observations (11)(A)(i) and (11)(A)(ii), respectively (see attachment 11A-D, (b) (4) The study covered the worst-case process flow and, therefore, the conclusions of the study can be applied to all LactoSorb products, not just the sampled LactoSorb plates and screws. The results of the study demonstrated that: (1) the viscosity of LactoSorb is stable over the course (b) (4) with a (b) (4) (b) (4) and (2) the LactoSorb product on the workbench is homogenous with respect to (a) time (b) (4) and (b) the viscosity (b) (4). In addition, a (b) (4) review was performed of data from (b) (4) data points for Lactosorb inherent viscosity. This was taken from (b) (4) sampled from (b) (4). A capability analysis was performed using (b) (4) (b) (4) (b) (4)). The results of this analysis showed (b) (4) (b) (4). There was one (b) (4) data point on (b) (4). This (b) (4). During this same (b) (4) (b) (4) lots of part number (b) (4) were subjected to inherent viscosity testing. Only (b) (4) (b) (4) However, (b) (4) (b) (4) Since they came from the (b) (4) this points to the mostly likely cause being a (b) (4)

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(b) (4). With this high level of capability, the sample size is sufficient and could even be reduced to a lesser (b) (4), Zimmer Biomet is (b) (4) (including the product identified in (b) (4) Observation 11(A)), as well as (b) (4) Zimmer Biomet opened Health Hazard Evaluation Determination ("HHED") #12-2016-008 to evaluate the (b) (4) and to determine the need to conduct a Health Hazard Evaluation ("HHE") (see attachment 11A-E, *HHED 12-2016-008*). (b) (4).

(b) (4)

Furthermore, Zimmer Biomet will (b) (4) plans to monitor the process control.

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Completed Actions:

No.	Action	Completion Date
11A-1	(b) (4)	September 20, 2016
11A-2	(b) (4) (see attachment 11A-C).	September 22, 2016
11A-3	Performed a study to evaluate and determine the homogeneity of the inherent viscosity of LactoSorb product (b) (4) (see attachment 11A-D).	October 3, 2016
11A-4	(b) (4) (see attachment 11A-A).	October 12, 2016
11A-5	Initiated CAPA CA-03082 to address the issues identified in Observation 11(A) (see attachment 11-A).	December 1, 2016
11A-6	Opened HHED #12-2016-008 to evaluate the potentia (b) (4) and to determine the need to conduct a Health Hazard Evaluation ("HHE") (see attachment 11A-E).	December 1, 2016

Planned Actions:

No.	Action	Completion Date
11A-7	Investigate outlier data point (b) (4) identified during (b) (4) review from (b) (4) data points for Lactosorb inherent viscosity.	(b) (4)
11A-8	Conduct root cause analysis for CAPA CA-03082 to determine why sampling plans identified in action 11-5 were used for inspections/release testing with insufficient statistical rationales.	(b) (4)
11A-9	Under CAPA CA-03082, determine if any additional containment actions are required following completion of root cause analysis for inspections/release testing with insufficient statistical rationales.	(b) (4)
11A-10	Under CAPA CA-03082, identify all procedures that define sampling plans for inspection/release testing used at Warsaw North Campus and determine if sufficient statistical rationale is available for.	(b) (4)
11A-11	Under CAPA CA-03082, identify sampling plans in use at the Warsaw North Campus for inspections/release testing that lack documentation of a sufficient statistical rationale.	(b) (4)
11A-12	Complete CAPA CA-03082 Root Cause/Action Plan Phase.	(b) (4)
11A-	Revise procedures, forms, and work instructions, as necessary, to	Target completion

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13	ensure the adequacy of statistical rationales for sampling plans.	date to be reported in a future update
11A-14	Complete CAPA CA-03082 Action Implementation Phase.	Target completion date to be reported in a future update
11A-15	Verify effectiveness of CAPA CA-03082 and close CAPA.	Target completion date to be reported in a future update

FDA Observation #11B

B. Sampling plans used in QP0010 Inherent Viscosity Testing for LactoSorb, Version 11 effective 05/03/2012, provide inadequate assurance that environmental exposure has not negatively impacted product quality. Inherent viscosity testing is performed on (b) (4) screws by sampling (b) (4) screw from the lot after sterilization; however, environmental exposure is not homogeneous throughout the lot and this sample selection is not representative of the population.

Interviews with a machining operator on 09/13/2016 revealed that machined LactoSorb screws are placed onto a tray that is exposed to the environment where they remain until machining operations are completed. The operator verified that the first screw had been exposed to the environment for (b) (4) hours while each screw produced thereafter had been exposed for subsequently less time. This operator was manufacturing a lot containing (b) (4) devices and, according to your firm's (b) (4) system, the minimum amount of time required to manufacture this lot would be (b) (4) hours.

According to a Note to File for the LactoSorb Vacuum Specification dated 2/23/2011, (b) (4) Your firm's Storage of (b) (4) In-Process" Product Process Engineering Specification 9.14 Rev. 10 dated 07/25/2016 states in section 4.2.3 to "Minimize uncontrolled environment exposure of "in-process product."

Observation 11(B) Investigation and Response:

As explained in the response to Observation 11 above, on December 1, 2016, Zimmer Biomet initiated CAPA CA-03082 to address the issues identified in the FDA-483 concerning the

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statistical rationale for sampling plans in use at the Warsaw North Campus (see attachment 11-A, *CAPA CA-03082 Summary*). CAPA CA-03082 is currently in the Investigation Phase. In addition to addressing system-wide corrective actions regarding statistical rationales for sampling plans, CA-03082 also addresses the specific findings in Observations 11(A) and 11(B) regarding the statistical rationale for sampling plans for lot acceptance for LactoSorb products.

As an (b) (4) in response to the Investigators' findings during the recent inspection, Zimmer Biomet(b) (4) , during the inspection (b) (4) . Additionally, Zimmer Biomet implemented (b) (4)

In addition, Zimmer Biomet performed a study to evaluate and determine the homogeneity of the inherent viscosity of LactoSorb product(b) (4) (see attachment 11A-C, (b) (4)). This study investigated the specific finding in Observation 11(B) regarding the testing of (b) (4) from a lot of (b) (4) finished LactoSorb devices that were exposed to the manufacturing conditions (including ambient humidity levels) for a variable duration, (b) (4) material. To determine whether there was any impact on the material and finished goods due to this sampling practice, (b) (4)

The results of the study show that the (b) (4) (b) (4)(b) (4) . (b) (4) (b) (4) (4) (b) (4) study demonstrate that:

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(b) (4) . In addition, a (b) (4) review was performed of data from (b) (4) data points for Lactosorb inherent viscosity. This was taken from (b) (4) sampled (b) (4) . A capability analysis was performed using (b) (4) ((b) (4) (b) (4)). The (b) (4) = (b) (4) There was one outlier data point on (b) (4) . This point was not out of specification, (b) (4) Since that time, the process has been highly stable and in control. (b) (4) is necessary. Finally, for (b) (4) , Zimmer Biomet opened Health Hazard Evaluation Determination ("HHED") #12-2016-008 to evaluate the potential impact to patients and to determine the need to conduct a Health Hazard Evaluation ("HHE") (see attachment 11A-E, *HHED 12-2016-008*). The conclusion of the HHED assessment was (b) (4) .

Please note that Zimmer Biomet is further reviewing the effects of manufacturing environment exposure on LactoSorb products in response to Observation 6(C). Zimmer Biomet will identify additional process controls, if any, for in-process LactoSorb product in response to Observation 6(C), and will provide information regarding additional corrective actions in future updates to that Observation.

Completed Actions:

No.	Action	Completion Date
11B-1	(b) (4)	September 20, 2016
11B-2	(b) (4)	September 22, 2016
11B-3	Performed a study to evaluate and determine the homogeneity of the inherent viscosity of LactoSorb product (b) (4) , as identified in Observation 11(B) (see attachment 11A-C).	October 3, 2016

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11B-4	(b) (4)	October 12, 2016
11B-5	Initiated CAPA CA-03082 to address the issues identified in Observation 11(B) (see attachment 11-A).	December 1, 2016
11A-6	Opened HHED #12-2016-008 to evaluate the potential impact to patients and to determine the need to conduct a Health Hazard Evaluation ("HHE") (see attachment 11A-E).	December 1, 2016

Planned Actions:

No.	Action	Completion Date
11B-7	Conduct root cause analysis for CAPA CA-03082 to determine why sampling plans identified in action 11-5 were used for inspections/release testing with insufficient statistical rationales.	(b) (4)
11B-8	Under CAPA CA-03082, identify all procedures that define sampling plans for inspection/release testing used at Warsaw North Campus and determine if sufficient statistical rationale is available for each.	(b) (4)
11B-9	Under CAPA CA-03082, determine if any additional containment actions are required following completion of root cause analysis for inspections/release testing with insufficient statistical rationales.	(b) (4)
11B-10	Under CAPA CA-03082, identify sampling plans in use at the Warsaw North Campus for inspections/release testing that lack documentation of a sufficient statistical rationale.	(b) (4)
11B-11	Complete CAPA CA-03082 Root Cause/Action Plan Phase.	(b) (4)
11B-12	Revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of statistical rationales for sampling plans.	Target completion date to be reported in a future update
11B-13	Complete CAPA CA-03082 Action Implementation Phase.	Target completion date to be reported in a future update
11B-14	Verify effectiveness of CAPA CA-03082 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation 12

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FDA Observation #12(A)

Procedures for rework of nonconforming product have not been adequately established.

Specifically,

A. Devices associated with 4 of 35 *Product Deviation/Reject Reports* ("deviations," *i.e.,* nonconforming product records) reviewed were reworked by the (b) (4) process, in which ultra-high-molecular-weight polyethylene (UHMWPE) components of UHMWPE/metal combination products that fail to meet acceptance criteria are (b) (4) . The following deficiencies were identified when reviewing the 4 deviations:

i. Your firm could not provide objective evidence that nonconforming product reworked by the (b) (4) process was reevaluated to determine whether device quality was adversely affected.

ii. Each of the 4 deviations reviewed were incorrectly dispositioned as "reprocess" rather than "rework". *SOP 13.0.1* (Rev. 15, effective 7/7/2016) defines "reprocess" as (b) (4) However, the (b) (4) " process is not within the DMRs of any part numbers associated with the 4 deviations. Consequently, the deviation was not approved by the (b) (4) as required by *SOP 13.0.1* in the event of rework.

iii. Your firm's Quality Director stated that use of the (b) (4) process was also approved by forms *INST 9.1 2.2.* However, the forms associated with each of the 4 deviations lack required approval signatures. Moreover, your firm's Quality Director confirmed that there exists no quality system procedure that governs the use of *INST 9.1.2.2* for the purpose of reworking or reprocessing nonconforming product.

iv. Your firm's Manufacturing Senior Engineer I stated that the (b) (4) process and subsequent acceptance activities ((b) (4)) are not defined by procedure. He confirmed that (b) (4) are not

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specified. Moreover, a (b) (4) step to remove any residual (b) (4) after (b) (4) has not been defined by procedure.

Observation 12(A) Investigation and Response:

(b) (4) During the recent inspection, CAPA CA-02645 was in the investigation phase. After the inspection, on November 22, 2016, Zimmer Biomet expanded the scope of CAPA CA-02645 to address system-wide issues concerning control of product that does not conform to specified requirements (see attachment 12A-A, *CAPA CA-02645 Summary*).

(b) (4)

To address the (b) (4) issue going forward, (b) (4) (b) (4) products on December 17, 2016, per Interim Control IC-035, "(b) (4) Additionally, per IC-035 (see attachment 12A-E, *IC-35 Nonconforming Product Procedure Interim Control*), all rework conducted via non-

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(b) (4) going forward, Zimmer Biomet will conduct a (b) (4) review of all nonconforming product reports ("NCRs") dispositioned as reprocess, rework, or UAI. Product will be escalated for formal containment (i.e., health hazard evaluation ("HHE")) as required by the (b) (4) review protocol.

Pursuant to CAPA CA-02645, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 12(A).
2. Eliminate planned deviations and non-standard rework and reprocessing, including:
   a. (b) (4)
3. Conduct a (b) (4) review of NCRs dispositioned as reprocess, rework, or UAI. Escalate product for formal containment (i.e., HHE) as required, per the (b) (4) protocol.
4. Review NCRs dispositioned and closed in (b) (4) to ensure the proper dispositioning of product and proper approval level.

In addition to the foregoing, pursuant to CAPA CA-02645, Zimmer Biomet will conduct a system-wide investigation of its procedures for controlling product that does not conform to specified requirements, as discussed in the response to Observation 3.

Completed Actions:

No.	Action	Completion Date
12A-1	Initiated (b) (4) of nonconforming product processes and practices.	June 7, 2016
12A-2	Revised SOP 13.0.1 to allow for appropriate deviation dispositions (b) (4)	June 2, 2016

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	(b) (4)	
12A-3	Initiated CAPA CA-02645 to address nonconforming product issues (see attachment 12A-A).	June 24, 2016
12A-4	Revised SOP 13.0.1 in connection with the planned implementation of (b) (4) (see attachment 12A-C).	November 11, 2016
12A-5	Incorporated INST 13.0.1.4 into SOP 13.0.1 and ensure form is attached to NCRs dispositioned as rework.	November 11, 2016
12A-6	Expanded the scope of CAPA CA-02645 to include system-wide procedures for controlling product that does not conform to specified requirements.	November 22, 2016
12A-7	Complete (b) (4) training of relevant personnel 12A-D).	December 12, 2016
12A-8	Ceased all rework of (b) (4) products (see attachment 12A-E).	December 17, 2016
12A-9	Implemented Interim Control IC-35 to discontinue (b) (4) (see attachment 12A-E).	December 17, 2016

Planned Actions:

No.	Action	Completion Date
12A-10	Complete root-cause analysis of the issues identified in Observation 12(A).	(b) (4)
12A-11	Review NCRs in (b) (4) for proper dispositioning and appropriate approval level of the assigned approvers.	(b) (4)
12A-12	Conduct a (b) (4) review of NCRs dispositioned reprocess, rework, or UAI. Escalate product for formal containment (i.e., HHE) as required per the (b) (4) review protocol.	(b) (4)
12A-13	Complete CAPA CA-02645 Investigation (Root Cause/Action Plan) Phase.	(b) (4)
12A-14	Complete CAPA CA-02645 Action Implementation Phase.	Target completion date to be reported in a future update
12A-15	Verify effectiveness of CAPA CA-02645 and close CAPA.	Target completion date to be reported in a future update

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FDA Observation #12(B)

B. Devices associated with 2 of 35 deviations (b) (4) *i.e.,* reworked) due to the presence of cosmetic defects. (b) (4) the process of (b) (4) The following deficiencies were identified when reviewing the 2 deviations:

i. Each of the 2 deviations reviewed were incorrectly dispositioned as "reprocess" rather than "rework". *SOP 13.0.1* (Rev. 15, effective 7/7/2016) defines "reprocess" as (b) (4) " The process of (b) (4) an untreated surface is within the scope of the relevant DMRs; however, the process of (b) (4) is not. Consequently, the deviation was not approved by the Quality Director, Product Development Director, and Regulatory Affairs Director as required by *SOP 13.0.1* in the event of rework.

ii. Each of the 2 deviations lacks documented evidence that the reworked nonconforming product was reevaluated to determine whether device quality was adversely affected.

Observation 12(B) Investigation and Response:

(b) (4)

Zimmer Biomet has ceased all rework associated with the (b) (4) process per Interim Control IC-035. Additionally, all non-validated, non-verifiable rework will cease per Interim Control IC-035 (see attachment 12A-E, *IC-35 Nonconforming Product Procedure Interim*

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Control). Zimmer Biomet also will conduct a (b) (4) review of nonconforming product reports ("NCRs"), (b) (4) .

Pursuant to CAPA CA-02645, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 12(B);
2. Eliminate non-standard rework and reprocessing, including:
   a. (b) (4)
3. Conduct a (b) (4) review of NCRs dispositioned reprocess, rework, or UAI. Escalate product for formal containment (i.e., health hazard evaluation ("HHE")) as required, per the (b) (4) review protocol.
4. Review NCRs dispositioned and closed in (b) (4) to ensure the proper dispositioning of product and proper approval level.

As noted previously, pursuant to CAPA CA-02645, Zimmer Biomet will conduct a system-wide investigation of its procedures for controlling product that does not conform to specified requirements, as discussed in the response to Observation 3.

Completed Actions:

For completed actions see above table list in observation 12a.

Planned Actions:

For planned actions see above table list in observation 12a.

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FDA Observation 13

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FDA Observation #13

Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established.

Specifically,

Your firm could not provide objective evidence that quality requirements have been communicated (b) (4) Tensile testing is to be performed as part of (b) (4) process monitoring per *QP001: Manufactured Poly Bar (b) (4) Testing Requirements* (Rev. 10, effective 12/18/2014). According to your firm's Associate Director of Biomaterials Research, the core of the bar stock is the worst-case location with respect to "material consolidation." Your firm could not provide objective evidence (b) (4) prepares tensile test specimens from this worst-case location.

Between 7/1/2014 and 10/13/2016, your firm distributed (b) (4) lots (total of (b) (4) devices) manufactured out of (b) (4) bar stock. In addition, between 7/1/2014 and 9/9/2016, your firm distributed (b) (4) inches of (b) (4) bar stock to other Zimmer Biomet facilities for their manufacturing of finished devices.

Observation 13 Investigation and Response:

On September 30, 2016, Zimmer Biomet initiated CAPA CA-02918 to address the issues identified in Observation 13 (see attachment 13-A, *CAPA CA-02918 CAPA Summary*). CAPA CA-02918 is in the investigation (Root Cause/Action Plan) phase.

Zimmer Biomet manufactures ultra high molecular weight polyethylene ((b) (4)) bar stock at its Warsaw North Campus. To test the (b) (4) bar stock's tensile strength, (b) (4) .
Observation 13 notes that during the inspection, Zimmer Biomet could not provide objective evidence that (b) (4) bar test specimens (b) (4) which is the worst-case location for material consolidation.

As an immediate correction, Zimmer Biomet issued a (b) (4) corrective action request (b) (4)) (b) (4) September 30, 2016 (see attachment 13-B, (b) (4)). The (b) (4) was issued due to lack of documented requirements for processing of tensile test specimens at

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(b) (4) (b) (4) Zimmer Biomet:

1. (b) (4) (b) (4)). Work orders completed to lock out (b) (4)

2. Manually "completed" its (b) (4) (b) (4) in the Zimmer Biomet (b) (4) which effectively blocked the (b) (4) and prevented any further (b) (4) (b) (4)

(b) (4), Zimmer Biomet developed procedures and specifications necessary to fully define the process for (1) preparing (b) (4) at Zimmer Biomet and (2) (b) (4) (b) (4). This included:

1. Developing tensile specification drawings (see attachment 13-D, *110032021-A-dwg1 (Rev. A*), and attachment 13-E, *110032021-01-dwg1 (Rev. A)*);
2. Implementing Interim Control IC-008 procedure for process monitoring of (b) (4) bar stock (see attachment 13-F, *IC-008 (Rev. 1)*);
3. Implementing a Work Instruction WI00233 for the preparation of (b) (4) bar segments (b) (4)) (see attachment 13-G, *WI00233 (Rev. 2)*); and
4. Revising quality assurance procedure QP0001 to make reference to both the new work instruction WI00233 and the new interim control process IC-008 (see attachment 13-H, *QP0001 (Rev. 12)*).

After developing these new procedures and specifications, (b) (4) (b) (4) verify compliance with the revised test specimen preparation specifications, including compliance with the requirement that test specimens (b) (4) (b) (4).

With respect to (b) (4) bar stock manufactured (b) (4), Zimmer Biomet determined that it was not impacted by the lack of objective evidence regarding the location within the bar from which test specimens were machined. This determination was outlined in a

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technical memorandum dated December 13, 2016, entitled (b) (4) (see attachment 13-K, *Technical Memorandum re:* (b) (4) . The technical memorandum details supporting data and rationale for the validity of the tensile testing data collected during the time when there was a lack of objective evidence (b) (4) (b) (4) .

On September 28, 2016,(b) (4) provided Zimmer Biomet with a description of the process (b) (4) used to prepare tensile test specimens and assurance (b) (4)). In addition, Zimmer Biomet's Biomet Mechanical Testing Laboratory measures and documents the cross-section dimensions (i.e., width and thickness) of each tensile test specimen prior to testing, (b) (4) ((b) (4)).

(b) (4)

.

Pursuant to CAPA CA-02918, Zimmer Biomet will complete documentation (procedures, specifications, etc.) as applicable for all non-inventory products and services that impact quality and lack the necessary documentation. Zimmer Biomet procedures did not require the company to evaluate whether a non-inventory, purchased product or service (b) (4)) could impact quality. The current procedure (b) (4) excludes most non-inventory items from its scope and lacks a defined process determining whether a non-inventory item or service may impact quality. Likewise, the supporting standard operating procedure ("SOP") (b) (4) does not apply to non-inventory items (b) (4) . In addition, the CAPA will include the following tasks:

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1. (b) (4)
   ;
2. Complete implementation phase of CAPA CA-02918; and
3. Verify effectiveness of CAPA CA-02918 and close the CAPA.

There are (b) (4) non-inventory items ((b) (4) (b) (4)) at the (b) (4). Zimmer Biomet conducted an initial evaluation of these non-inventory items to identify other quality-impacting (b) (4) products or services with lack of defined quality specifications and requirements (b) (4)

The evaluation concluded that (b) (4)

. Once the final evaluation is complete, and it is determined whether (b) (4) are impacted, quality documentation (procedures, specifications, etc. as applicable) will be created for those (b) (4) of non-inventory products and services that impact quality and currently lack the necessary documentation.

Completed Actions:

No.	Action	Completion Date
13-1	(b) (4)(b) (4) (b) (4) review and document the process of producing tensile test specimens (b) (4) (b) (4)	September 28, 2016
13-2	Initiated CAPA CA-02918 to address the issues identified in Observation 13 (see attachment 13-A, *CA-02918 CAPA Summary*).	September 30, 2016
13-3	Issued (b) (4) due to lack of documented requirements for processing of tensile test specimens (b) (4) (see attachment 13-B, (b) (4)).	September 30, 2016
13-4	(b) (4) (b) (4)	October 13, 2016

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	(b) (4)	
13-5	(b) (4) (b) (4) while an interim control could be implemented.	October 14, 2016
13-6	Developed procedures and specifications necessary to fully define the process for preparing test blanks (b) (4) and test specimens (b) (4) including tensile specification drawings (b) (4)) bar segments (b) (4)) (see attachment 13-G) and revised quality assurance procedure to make reference to both the new work instruction WI00233 and the new interim control process IC-008 (see attachment 13-H).	October 25, 2016
13-7	Resumed (b) (4) (b) (4) (see attachment 13-I).	October 26, 2016
13-8	(b) (4) (b) (4) to verify compliance with revised test specimen preparation specifications, including compliance with requirement that test specimens (b) (4) (see attachment 13-J).	October 27, 2016
13-9	(b) (4)	December 13, 2016
13-10	Conducted initial evaluation of (b) (4) non-inventory items (b) (4)	December 16, 2016

Planned Actions:

No.	Action	Completion Date
13-11	As part of CAPA CA-02918, revise (b) (4) procedures (1) to define requirements for (b) (4) non-inventory products and services for quality impact and to ensure creation of quality specifications and procedures where applicable going forward as (b) (4) are added to the (b) (4)	(b) (4)
13-12	As part of (b) (4) (b) (4) (b) (4)	(b) (4)
13-13	As part of CAPA CA-02918, complete final evaluations to identify (b) (4) of non-inventory products and services that have quality impact and are currently lack the necessary	(b) (4)

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	quality documentation.	
13-14	Create quality documentation (procedures, specifications, etc. as applicable) for (b) (4) (b) (4) non-inventory products and services that impact quality and currently lack the necessary documentation.	Target completion date to be reported in a future update
13-15	Complete CAPA CA-02918 Root Cause / Action Plan Phase.	(b) (4)
13-16	Complete implementation phase of SCAR-01181.	Target completion date to be reported in a future update
13-17	Verify effectiveness of (b) (4) and close the (b) (4)	Target completion date to be reported in a future update
13-18	Complete implementation phase of CAPA CA-02918.	Target completion date to be reported in a future update
13-19	Verify effectiveness of CAPA CA-02918 and close the CAPA.	Target completion date to be reported in a future update

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FDA Observation 14

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FDA Observation #14

Document control procedures have not been adequately established.

Specifically,

Procedures to control changes to Master Routing Files *(i.e.,* DMRs) have not been adequately established. Specifically, on 08/25/2016, a new CNC machining program number (LM3175) was added to the DMR of an (b) (4) patellar implant (item number 11-150828). This change was not documented and approved according to *SOP 5.3.1: Change Control Procedure* (Rev. 8, effective 3/6/2015), which states "Changes made to a master Routing File, are processed in accordance with QM 9.1 Routing Procedures." *QM 9.1* (Rev. 8, effective 6/28/2016) states "Manufacturing Engineering is responsible for approving changes to the Routing(s) in accordance *with INST 9.1.2.2* Routing and Manufacturing Order (MO) form." Your firm was unable to provide evidence that a form *INST 9.1.2.2* associated with this change was completed and approved prior to the change being made on the DHR. During an interview on 9/13/2016, an operator on the manufacturing floor explained that she was made aware of the change to the DHR verbally.

Observation 14 Investigation and Response:

During the recent inspection, on September 19, 2016, Zimmer Biomet initiated CAPA CA-02866 to address the change control issues identified in Observation 14 (see attachment 14-A, *CAPA CA-02866 Summary*). As noted in Observation 14, inspectors observed that an operator at Work Center (b) (4) had been given verbal approval to use a Computer Numerical Control ("CNC") machining program (Program #LM3175) in the manufacture of an (b) (4) implant (Item #11-150828). Although use of the CNC machining program had been added to the device master record ("DMR") for the (b) (4) patellar implant, the approval to use the CNC machining program was not documented as required. CAPA CA-02866 currently is in the investigation (Root Cause/Action Plan) phase. In addition, on December 13, 2016, Zimmer Biomet initiated CAPA CA-03125 (Quality System Change Control CAPA) to address system-wide issues concerning control of changes to a document, specification, method, process, or procedure at the Warsaw North Campus (see attachment 14-B, *CA-03125 Summary*). CA-03125 also currently is in the investigation (Root Cause/Action Plan) phase.

As an initial containment measure, on September 13, 2016, Zimmer Biomet reviewed the device history record ("DHR") for Lot #M570370 of the (b) (4)patellar implant (Item #11-150828). The DHR showed that (b) (4)

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(b) (4)

Zimmer Biomet issued a (b) (4) (b) (4) that was (b) (4) (b) (4)) (see attachment 14-D, (b) (4)). The (b) (4) for the product on (b) (4) (see attachment 14-E, (b) (4)). Until the (b) (4) has been (b) (4) (b) (4)).

As part of this effort, Zimmer Biomet reviewed the process by which CNC machining programs are created, reviewed, and released for use in operations ((b) (4) to identify gaps (b) (4) In addition, on November 14, 2016, Zimmer Biomet conducted a quality records search to identify any issues related to the machining program change control process. The (b) (4) On December 13, 2016, Zimmer Biomet documented the addition of CNC machining program program #LM3175 via a manufacturing order form (see attachment 14-J, *INST 9.1.2.2 for Addition of LM3175 Program*).

On December 13, 2016, Zimmer Biomet conducted a search in the (b) (4) database to identify all lots of the (b) (4) patellar implant (Item #11-150828) that were produced without a documented CNC program between (b) (4) (when CNC program LM3175 was released) (b) (4) . The results of this search revealed that (b) (4) of the (b) (4) patellar implant were manufactured at Work Center (b) (4) during that (b) (4) . Zimmer Biomet (b) (4) (b) (4) (b) (4)

Pursuant to CAPA CA-02866, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Conduct a root-cause analysis of the issues identified in Observation 14;
2. Develop an implementation plan for CAPA CA-02866; and
3. Develop a verification of effectiveness ("VoE") plan for CAPA CA-02866.

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With respect to (b) (4)) that were produced without a documented CNC program, Zimmer Biomet initiated a health hazard evaluation-determination ("HHED") on December 16, 2016 (see attachment 14-L, *HHED 12-2016-022*). The HHED process resulted in (b) (4)

Additionally, pursuant to CAPA CA-03125, Zimmer Biomet will conduct an investigation that includes the following tasks:

1. Review existing procedures, forms, and work instructions associated with change controls at the Warsaw North Campus and ensure that they are compliant with the requirements of 21 C.F.R. §§ 820.40 and 820.70(b);
2. Develop an implementation plan for CAPA CA-03125; and
3. Develop a VoE plan for CAPA CA-03125.

Zimmer Biomet will revise procedures, forms, and work instructions, as necessary, to ensure the adequacy of change control quality system requirements.

Completed Actions:

No.	Action	Completion Date
14-1	Reviewed the DHR for (b) (4) and (b) (4)	September 13, 2016
14-2	Initiated CAPA CA-02866 to address the change control issues identified in Observation 14 (see attachment 14-A).	September 19, 2016
14-3	Issued NCR for (b) (4) that (b) (4) (see attachment 14-D).	September 22, 2016
14-4	Issued second NCR for (b) (4) (see attachment 14-E).	October 13, 2016
14-5	Conducted a quality records search to identify any issues related to the machining program change control process (see attachment 14-I).	November 14, 2016
14-6	Reviewed the process by which CNC machining programs are created, reviewed, and (b) (4) (b) (4)).	December 8, 2016
14-7	Initiated CAPA CA-03125 to review change control processes (see attachment 14-B).	December 13, 2016
14-8	Conducted a search in the enterprise database to identify all lots of Item #11-150828 manufactured at Work Center (b) (4) between (b) (4) (when CNC program LM3175 was released) and (b) (4) (see attachment 14-K).	December 13, 2016
14-9	Documented the addition of CNC machining program program	December 13, 2016

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	#LM3175 via a manufacturing order form (see attachment 14-J)	
14-10	(b) (4) pending the outcome of this investigation (see attachments 14-F).	December 15, 2016
14-11	Initiated HHED for (b) (4)) that were produced without a documented CNC program (see attachment 14-L).	December 16, 2016

Planned Actions:

No.	Action	Completion Date
14-12	Complete CAPA CA-2866 Investigation (Root Cause / Action Plan) Phase.	(b) (4)
14-13	Complete CAPA CA-3125 Investigation (Root Cause / Action Plan) Phase.	(b) (4)
14-14	Complete CAPA CA-02866 implementation phase.	Target completion date to be reported in a future update
14-15	Verify effectiveness of CAPA CA-02866 and close CAPA.	Target completion date to be reported in a future update
14-16	Review existing change control processes at the Warsaw North Campus and evaluate their compliance with 21 C.F.R. §§ 820.40 and 820.70(b).	Target completion date to be reported in a future update
14-17	Complete CAPA CA-03125 implementation phase.	Target completion date to be reported in a future update
14-18	Verify effectiveness of CAPA CA-03125 and close CAPA.	Target completion date to be reported in a future update