DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313)393-8139	9/12/2016-11/22/2016* FEI NUMBER 1825034

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

David J. Kunz , Senior Vice President, Global Quality Assurance, Regulatory Affairs, and Clinical Affairs

FIRM NAME	STREET ADDRESS
Zimmer Biomet, Inc.	56 E Bell Dr.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Warsaw, IN 46582	Medical Device

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

The observations noted in this Form FDA-483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

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 WIS0086 (Rev. 3, effective 10/13/2015) for sports medicine and microfixation devices manufactured out of*** (b) (4) ***and*** (b) (4) ***materials***
- ***I. Ultra-high-molecular-weight polyethylene (UHMWPE)*** (b) (4) ***molding process validation***

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SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	DATE ISSUED
	Thomas A Peter, Investigator Joseph R Strelnik, Investigator Suyang Qin, Investigator 11/22/2016 X Thomas A Peter Thomas A Peter Invest gator Signed by: Thomas A. Peter -S	11/22/2016

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A. The "metals" family sterilized by (b) (4) has not been adequately validated to provide objective evidence that sterilized devices meet a SAL of (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 in 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) unique item numbers that were distributed between 7/1/2014 and 10/13/2016. These (b) 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) 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) During the study, your firm chose five different devices (item numbers) for comparison against the simulated product. However, a

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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) have no documented assessment of whether they introduce a greater sterilization challenge than the simulant. Approximately (b) (4) devices with these (b) 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 (b) (4) unique item numbers until after that date. (b) (4) item numbers (b) have no documented assessment associated with them. Approximately (b) (4) devices with these (b) 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) 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 (b) (4) lines commissioned in (b) (4) were located in the (b) (4) (b) (4)). As of 9/12/2016, the simulated product (CP550157) continues to be (b) (4) in (b) (4) before being inspected in (b) (b) (4) and packaged in (b) (4) .

From the time the simulated product was approved on 3/17/2003 to 10/25/2016, the metals family has evolved into approximately (b) 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)	Subsequent Processing Steps

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	Work Center	
Vanguard CR knee porous femoral components (*e.g.*, item number 183056)	(b)	• Inspection (b) (4) • Assembly (b) (4) • Inspection (b) (4) • Packaging (b) (4)
Vanguard XP CR tibial trays (*e.g.*, item number 195273)	(b)	• Inspection (b) (4) • Packaging (b) (4)
Freedom Hip System constrained modular head component (*e.g.*, item number 110025131)	(b)	• Inspection (b) (4) • Packaging (b) (4))
Regenerex acetabular shell (*e.g.*, item number PT-126272)	(b)	• 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) 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) item numbers comprising the family were distributed by your firm between 7/1/2014 and 10/13/2016.

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:

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1. The reports included trend analyses 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 (b) (4) 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 environments to which devices are exposed after (b) (4) have changed over time.

B. 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 (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:

   i. 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.

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ii. 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.

iii. 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) (b) (4). During the (b) (4) cycle and (b) cycles, your firm placed (b) product samples and (b) IPCDs within (b) totes throughout the sterilization load. However, the location within each tote was not defined.

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

a. 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 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.

b. During requalifications since at least 2008, your firm has assembled IPCDs in a manner that apparently renders (b) (4) than in earlier requalifications and the initial validation. Products sterilized by (b) (4) are packaged in configurations such (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) with the product. Beginning in 2008, IPCDs were assembled by (b) (4) (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.

v. 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) (b) 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) .

C. 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:

i. Your firm's Package System Validation Corporate Biomet Procedure, CP1516 Rev. 1 effective 12/17/2010, references conformance to EN 868-5:2009, whic (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 contracted 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) 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 (b) (4), and (b) did not utilize actual or simulated product in the runs. For example, the Performance Qualification for die SD011-2.2, packaging configurations (b) (4) 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) 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 (b) (4) did not include a minimum of (b) (4) production runs. For example, your firm's Die Validation Testing Report for (b) (4) (b) (4) /Suture Anchor Tray approved 2/22/2010 only utilized (b) (4) lot of (b) (b) 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:

1. Utilize (b) (4) operators (b) (4) to account for person to person variation. For example, your firm's die validation for die (b) (4) /Suture Anchor Tray on sealer (b) approved on 02/22/2010 included (b) (4)
b b

2. 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 (b) 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 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)

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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) 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.

Historically, packaging sealer/die information was not documented in DHRs or any other reference documents for sealers (b) (4). Your firm began documenting this information for these sealers on 09/26/2016, 08/10/2016, 09/14/2016, and 09/06/2016 respectively. As of 11/01/2016, your firm has distributed (b) devices that were packaged on these sealers; examples of product families packaged with these sealers and distributed include (b) (4). Prior to the aforementioned dates, your firm was unable to provide distribution information for devices packaged on these sealers upon request. From 07/01/2014 to 11/01/2016, these sealers have been used in cleanrooms to seal terminally sterilized devices.

D. 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) (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:

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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. 1 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) 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.

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(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) . (b) (4) Water supplied from the (b) 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) mg/L, Conductivity (b) µS/cm at (b °C, Endotoxins "Optional" (b) EU/ml, and Total Heterotrophic Count (b) CFU/ml. However, the section also notes the following:

1. (b) (4)

2. (b) (4)

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

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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 29 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) mg/L in 28 out of 29 samples.
   b. The Conductivity specification of (b) µS/cm at (b) °C in 0 out of 29 samples.
   c. The Endotoxins specification of (b) EU/ml in 1 out of 29 samples.
   d. The Total Heterotrophic Count specification of (b) 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) mg/L in 28 out of 29 samples.
   b. The Conductivity specification of (b) µS/cm at (b) °C in 21 out of 29 samples.
   c. The Endotoxins specification of (b) EU/ml 0 out of 29 samples.
   d. The Total Heterotrophic Count specification of (b) CFU/ml in 0 out of 29 samples.

The Results Assessment section of the water system validation report concluded, in part, (b) (4) [redacted]."

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

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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) and (b) water. These units have a maximum flow rate of (b) gallons per (b) (4) and maximum operating pressure of (b) psi. Your firm has no objective evidence that those requirements have been met.

ii. Your firm's (b) (4) Water System Validation – Biomet (b) 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) mg/L, Conductivity (b) µS/cm at (b) °C; pH within (b) (4) , Endotoxins (b) EU/ml, and Total Count (b) CFU/ml. However, the section also notes the following:

1. (b) (4)

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2. Note 1 states (b) (4) [redacted]

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) systems will be sanitized once (b) (4) .

c. Your firm's (b) (4) Water System Addendum to Validation Report for the Biomet (b) Water System approved on 10/16/2007 included (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 Failures	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

E. Your firm's (b) (4) 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 (b) (4) ," (b) (4) . The following deficiencies were identified when reviewing Validation #118:

i. 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 (b) %. However, a minimum detergent concentration of (b) % was used during the validation.

ii. 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.

iii. (b) (4) . 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.

iv. Your firm's Manufacturing Manager explained that the (b) (4) tanks are drained and refilled with (b) (4) solution at (b) (4) , however, the number of devices cleaned (b) (4) may vary. A maximum number of devices that may be cleaned between tank refills was not established or challenged during the validation.

v. 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.

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vi. 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.

F. Your firm's manual cleaning process used to clean metal hip, extremities, knee, trauma, microfixation, and sports medicine devices as governed by work instruction *WIG0151* (Rev. 1, 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: (b) (4) The following deficiencies were identified when reviewing Validation #141:

i. 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.

ii. The validation protocol (approved 11/19/2010) states that (b) (4) 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 *WIG0151* (Rev. 1, effective 4/21/2015), which describes how to use "approved chemicals" (*e.g.*, (b) (4) solvent and (b) (4) alcohol) 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.

iii. 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 (b) (4) approved chemicals which may be used.

iv. 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.

v. 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 (b) (4) and that a separate manual cleaning validation that omits (b) (4) does not exist.

vi. *WIG0151* (Rev. 1, effective 4/21/2015) allows the use of a (b) (4) cleaner and/or (b) 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.

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vii. Several parts of *WIG0151* (Rev. 1, 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)

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

G. Your firm's manual cleaning process for devices made of ultra-high-molecular-weight polyethylene (UHMWPE) by submersion in a bath of (b) (4) 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):

i. *WIG0150* (Rev. 3, effective 5/4/2016) requires a submersion time of (minutes (b) (4) (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.

ii. While watching the cleaning operation on 9/14/2016, the operator explained that (b) baths are drained and refilled (b) (4) and that there is no limit to the amount of devices that may be placed in the bath in a (b) (4) . A maximum number of devices that may be cleaned between bath refills was not established or challenged during the validation.

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iii. 12 devices (b) (4) were tested for bioburden, endotoxin, and cytotoxicity during the validation. Statistical rationale for this sampling plan was not documented.

iv. Section A, Step 3 of *WIG0150* instructs operators to (b) (4) after soaking devices in the (b) 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 (b) (4) devices that were cleaned via this process.

H. Your firm's (b) (4) cleaning process governed by work instruction *WIS0086* (Rev. 3, effective 10/13/2015) for sports medicine and microfixation devices manufactured out of (b) (4) and (b) 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 (b) (4) used during compression and injection molding. The following deficiencies were identified when reviewing Validation #184:

i. 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 (b) (4) bath temperature range of (b) (4) C.

ii. 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 (minutes per cycle (b cycles). As such, your firm could not provide objective evidence that a worst-case condition of (minutes per cycle was challenged.

iii. When witnessing the process on 9/14/2016, we observed that the (b) (4) cleaner was set to a power (*i.e.*, (b) (4)) setting of (b) which could be manipulated by the operator. A required power setting was

not established or challenged during the validation.

iv. 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 (b) (4) during the cleaning process. The actual devices masses and (b) (4) volumes used during the validation were not documented. As such, your firm could not provide objective evidence that worst-case solvent volume of (b) (4) was challenged.

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

I. Your firm's (b) (4) molding process used to manufacture (b) (4) bar stock out of (b) (4) failed to meet acceptance criteria during validation. (b) (4) Your firm manufactures (b) (4) bar stock of several different diameters, with the (b) version being the largest. The (b) (4) bar stock is manufactured out of (b) (4) which presented the greatest challenge during Validation #42, Addendum #1 (approved 2/22/2010) because (b) (4) During the validation, (b) (4) used to manufacture (b) (4) bar stock out of (b) (4) failed to meet mechanical testing acceptance criteria. Despite this, your firm continues to manufacture (b) (4) (b) (4) bar stock as of 9/9/2016. *QP0001* (Revs. 6 through 10; effective 3/17/2010 to 10/20/2016) requires that for "non-validated" item numbers such as (b) (4) (*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 (b) (4) historically been tested from each lot. This practice is inadequate to assure the bar stock meets all quality requirements because the (b) (4) molding process is not fully verifiable.

Between 3/1/2010 and 9/19/2016, your firm distributed at least (b) devices manufactured out of (b) (4) (b) (4) bar stock. Also, between 3/1/2010 and 11/1/2016, your firm distributed (b) inches of (b) (4) (b) (4) bar stock to other Zimmer Biomet facilities for their manufacturing of finished devices.

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313)393-8139	9/12/2016-11/22/2016*
	FEI NUMBER 1825034

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

David J. Kunz , Senior Vice President, Global Quality Assurance, Regulatory Affairs, and Clinical Affairs

FIRM NAME	STREET ADDRESS
Zimmer Biomet, Inc.	56 E Bell Dr.
CITY, STATE, ZIP CODE, COUNTRY Warsaw, IN 46582	TYPE ESTABLISHMENT INSPECTED Medical Device

OBSERVATION 2

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) (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

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) ((b) (4)

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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 (1) 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) Cleanroom Gowning Room (b) (4) in samples collected from the (b) (4) hand-washing sinks.

Procedure	Date	Test Failed	Alert/Action Limits	Sample Result	Retest Value
QP0021	7/21/14	Microbial - (b)	(b) (4)	64	1
QP0024	7/21/14	Endotoxin - (b)	(b) (4)	0.314	0.0125
QP0024	07/21/14	Endotoxin - (b)	(b) (4)	0.369	0.0726

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:
b

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) (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) CFU/ml and (b) CFU/ml while the b ndotoxin alert and action limits became (b) EU/ml and (b) 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 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.

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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 (b) 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 (b) (4) 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 (b) feet away from each other on opposite sides of the room. These locations are as follows:

1. (b) (4) [redacted]
2. (b) (4) [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 (b) (4) Packaging Cleanroom, (b) (4) represents a total area of (b) square feet ((b) square meters). Per the standard, the minimum number of sample locations must be (b) In this cleanroom, your firm has identified and routinely monitors nine (9) sampling locations, which represents approximately (b) % of the required number. There is no documented rationale for using this number of sampling locations.

2. The (b) Cleanroom, (b) (4) is used to package all (b) (4) metals products (b) (4) and represents a total area of (b) square feet ((b) square meters). Per the standard, the minimum number of sample locations must be (b). In this cleanroom, your firm has identified and routinely monitors (9) sampling locations, which represents approximately (b) % 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 (b) (4) Maps of routine sampling locations are not drawn to scale and do not provided objective evidence that (b) (4). 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 (b) (4). Review of settings for your firm's particle counter (Asset (b) (4), model (b) (4)) 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 micro-organisms. 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 (b) WE. All three (3) fans were visibly soiled with apparent grayish dust/debris with one (1) blowing onto the operator approximately 12" above lot# (b) (4) (b) (4)) that

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was just removed from an (b) (4) cleaning bath.

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 off-loaded. b

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 these excursions revealed that 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	08/21/14	Microbial Air and Surface	6	(b) (4)
(b) (4)	Cleanroom	11/19/14	Microbial Air and Surface	4	(b) (4)
(b) (4)	Cleanroom	08/21/14	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)	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)	Work Env.	06/16/16	Microbial Air	(b) CFU	(b) CFU	(b) CFU

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

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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 (b) (4) WE, there is a (b) (4) (b) (4) line and subsequent inspection step. Product families passing through this WE (b) (4)) include (b) (4) However:

   i. The (b) (4) line is open to the uncontrolled manufacturing environment on one side to (b) (4) . Air flow passes through a HEPA filter above the inspection table, but is supplied by the main HVAC 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, (b) (4) 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 (b) (4) . Your firm's alert/action limits for surface monitoring are (b) CFU and (b) CFU while the microbial air monitoring is (b) CFU and (b) CFU

2. For the (b) (4) (b) (4)), ((b) (4) Product families passing through this WE include (b) (4) However:

   i. The room is physically separated from uncontrolled environments by slatted plastic curtains, but the dedicated HVAC system that supplies the room with air flow utilizes (b) (4) located in a hallway in an uncontrolled

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environment outside of the WE. The air vents that supply air to this room are not filtered by HEPAs.

ii. INST 9.5.8.12 rev. 1 requires (b) (4) . 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 (b) (4) Your firm's alert/action limits for surface monitoring are (b) CFU and (b) CFU while the microbial air monitoring is (b) CFU and (b) CFU

3. For the (b) (4) (b) (4) , an (b) (4) (b) (4) line off-loads carriers containing exposed devices to the WE. Product families passing through this WE include (b) (4) . However:

i. The room is physically separated from uncontrolled manufacturing environments by hard walls and doors. The dedicated HVAC 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 (b) rooms are HEPA filtered.

ii. INST 9.5.8.12 rev. 1 requires (b) (4) . 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 (b) (4) Your firm's alert/action limits for surface monitoring are (b) CFU and (b) CFU while the microbial air monitoring is (b) CFU and (b) CFU

b. Your firm identifies Resorbable Tech (b) (4) , Sports Med (b) (4) , and Bag Mfg. (b) (4) as controlled environments, but they do not share the similar levels of control. For example:

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1. Per INST 9.5.9.19 rev. 3 effective 8 Jan 2015, the Biomet Sports Medicine Controlled Environment Room (b) (4) requires Surface Monitoring (Contact Plates) and Air Sampling (Air Strips) to be monitored (b) (4)

2. Per INST 9.5.9.17 rev 3 effective 30 Dec 2014, the Resorbable Tech Controlled Environment Room (b) (4) requires Cleaning to be performed (b) (4))

3. Per INST 9.5.9.15 rev. 11 effective 06/11/2015, the Bag Manufacturing Controlled Environment (b) (4) requires Differential Pressure, Temperature, and Relative Humidity to be monitored (b) ; Particulate Counts, Air Flow – Supply, and Air Flow – Return to be monitored (b) (4) and Surface Monitoring (Contact Plates) and Air Sampling (Air Strips) to be monitored (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)

OBSERVATION 3

Procedures have not been adequately established to control product that does not conform to specified requirements.

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 (b) (4)

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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 (b) Cleanroom (b) (4) explained that employees use (b) 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 (b) % 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 (b) (b) , as stated by the Manufacturing Supervisor of that area on 9/13/2016. Between 7/1/2014 and 9/9/2016, only (b) % of all devices packaged in (b) (4) were done so in the Sports Medicine Department of cleanroom (b) (4) ((b) (4) devices).

ii. Outside of the Sports Medicine Department in (b) (4) interviews with operators from several areas throughout (b) (4) revealed additional instances of nonconforming product not routinely being documented as deviations. For example:

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

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ii. In the (b) (4) Work Environment, Cleaning Operators cited knee femoral implants found notably soiled after passing through the (b) (4) ultrasonic cleaner.

iii. In the (b) Cleaning/Inspection Work Environment, Cleaning Operators cited parts that are still soiled after performing validated cleaning operations.

iv. In the (b) (4) , Machining Operators cited hip stem tapers that do not meet specification.

v. In the (b) (4) Area, (b) (4) Inspection Operators cited bars with areas of perceived unconsolidation or inherent defects

C. Since 2/8/2012, 4 routine loads sterilized by (b) (4) sterilization (b) (4) 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	(b) (4)	(b)
10213-G	11/5/2013		(b)
11203-C	12/9/2013		(b)

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 11/16/2016) and subsequently distributed. Notably, the BIs tested during routine sterilization are located on the outside of the (b) (4) 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.

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. You 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.

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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.

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 (b) (Run-at-Risk #2016-003, effective 5/2/2016 to 7/2/2016). (b) 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.

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) . Of the (b) lots (b) devices) packaged using sealer (b) 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) 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 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) sealers. 1 of the (b) forms indicated that on 9/24/2016, Sealer (b) (4)

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was operating outside of the parameter ranges specified by *Process Engineering Specification 1.31* (Rev. 91., effective 9/20/2016). The(b 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) devices) (*e.g.*, Vanguard knee tibial bearings with item number 183724, tibial plates with item number 814133002, and Jugger-loc sports medicine devices with item number 110010372) had been distributed at the time of this inspection.

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 #11 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) bar lot and released the lot after the retests met tensile strength specifications. Justification for accepting the entire lot of (b) bars based on the test results of (b) bars was not documented. Moreover, the deviation failed to provide evidence that tensile test samples were prepared from the core of the (b) 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) , but this testing was never performed. As such, your firm was unable to provide objective evidence that the (b lots of (b) (4) bar stock manufactured in Vessel (b) 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) devices manufactured out of the (b) lots of bar stock. Additionally, as of 9/9/2016, your firm distributed (b) inches of the (b) lots of bar stock to other Zimmer Biomet facilities for their manufacturing of finished devices.

OBSERVATION 4

Procedures for design control have not been established.

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DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313)393-8139	9/12/2016-11/22/2016* FEI NUMBER 1825034

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

David J. Kunz , Senior Vice President, Global Quality Assurance, Regulatory Affairs, and Clinical Affairs

FIRM NAME	STREET ADDRESS
Zimmer Biomet, Inc.	56 E Bell Dr.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Warsaw, IN 46582	Medical Device

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) item numbers (b) implant item numbers and (b) instrument item numbers):

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

   i. (b) (4) our 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) of the (b) implant item numbers (approximately (%) within the scope of the design project.
   b

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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) includes "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:

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)

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(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 "IO 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:

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

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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 (MT2656)" (dated 8/22/2002), your firm determined the tibiofemoral contact area for 4 different femoral component/tibial bearing combinations:

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

While reviewing this design verification study, we observed that:

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 (b) (4) 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 (b) times at each of (b) (4) .

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)

(b) (4)

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* (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 5

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

Specifically,

A. *CP1409: 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. *CP1409* 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." *CP1406* (Rev. 5, effective 9/1/2015) 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 records) 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.

(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.

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 capture the development of multiple (b) (4) sterilization product

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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 1(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) (4) cycle (b) (b) validation, we observed the existing nonconformances described in Observation 1(B).

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 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 6

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

Specifically,

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313)393-8139	9/12/2016-11/22/2016* FEI NUMBER 1825034

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

David J. Kunz , Senior Vice President, Global Quality Assurance, Regulatory Affairs, and Clinical Affairs

FIRM NAME	STREET ADDRESS
Zimmer Biomet, Inc.	56 E Bell Dr.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Warsaw, IN 46582	Medical Device

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) 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) production lots of Mimix microfixation devices on Sealer (b) using die (b) (4) with parameters that were not validated for use when the equipment was moved from (b) (4) to (b) (4) (b) of these lots consisting of (b) 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) (b) psi for optimal temperature and dwell settings of (b) °F and (b) seconds respectively. The validation concluded that nominal settings for the machine were (b) °F (b) seconds, and (b) psi, but these settings were never transferred to PES 1.31. When the (b) 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) °F, (b) seconds, and (b) 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): (b) (4) and

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(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 psi. One (1) out of seven (7) of the dies provided a minimum air pressure of (b psi,) but a maximum air pressure of N/A when both should be (b psi.
2. Two (2) out of nine (9) dies listed in 1.31 incorrectly identify the maximum validated range for dwell time as (b) when the corresponding validations for those dies used (b) seconds.

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 betwee (b) (4) . During the interview, we observed:

a. We observed a bottle of (b) (4) in Work Center (b) , which the operator explained he uses to remove any debris seen on (b) (4) femoral implants. Use of the (b) is not discussed in *WIG0160*. The operator explained that he works in Work Center (b) "every day" and uses (b) 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) . Use of (b) (4) is not discussed in *WIG0160*. The operator explained that he always uses (b) instead of (b) (4) but was unsure if any other operators who work in Work Center (b) 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.

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

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

ii. Work instruction *WIS0086* (Rev. 3, effective 10/13/2015), which governs ultrasonic cleaning of sports medicine and microfixation devices manufactured out of (b) (4) and (b) 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) 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) 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 (b) (4) devices that were cleaned via this process.

iii. Work instruction *WIG0150* (Rev. 3, effective 5/5/2016), which governs manual 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) (b) (4) devices ((b) (4) into an (b) bath while performing this cleaning operation. He stated there was no limit to the amount of devices that may be placed in the bath and that "there's not enough room" for devices to not contact one another.

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b. Your firm's Packager stated that (b) 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) (b) *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. 1, 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.

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 1.5 mm x 4 mm screws, item 915-2315-01 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:

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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) screws. According to your firm's (b) system, the minimum amount of time needed to manufacture (b) screws would be (b) 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 7

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

Specifically,

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

Procedures for cleaning process monitoring have not been adequately established. For example, (b) (4) testing performed on metallic devices per *QP0026:* (b) (4) (Rev. 6, effective 11/19/2014) is inadequate in that:

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:
(b)
(

B. Two of the (b) 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.

AMENDMENT 1

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)) is approximately (b) % larger than the porous surface area of the simulated product CP550157 used during cleaning process monitoring ((b)).

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) 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 (processing lines:
   i. Devices processed through the (b) (4) cleaning process and (b) (4) line(s)
   ii. Devices processed through the (b) (4) 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 and (b) (4) lines" (Work Center (b))
   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) 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 (b) (4) devices were manufactured via this processing line. (b) (4) devices have been distributed as of 9/9/2016.

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DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
300 River Place, Suite 5900 Detroit, MI 48207 (313) 393-8100 Fax:(313)393-8139	9/12/2016-11/22/2016*
	FEI NUMBER 1825034

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

David J. Kunz , Senior Vice President, Global Quality Assurance, Regulatory Affairs, and Clinical Affairs

FIRM NAME	STREET ADDRESS
Zimmer Biomet, Inc.	56 E Bell Dr.
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Warsaw, IN 46582	Medical Device

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.

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 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.

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	Thomas A Peter, Investigator Joseph R Strelnik, Investigator Suyang Qin, Investigator 11/22/2016 X Thomas A Peter Thomas A Peter Investigator Signed by: Thomas A. Peter -S	11/22/2016

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OBSERVATION 9

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 device (b) (4) However, on 09/12/2016, we observed an operator verify the overall (4) (4) 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) inches that would pass final inspection. This worst-case thickness is (b) % less than the minimum specification of (b) 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) (b) (4) devices reviewed during this inspection. Specifically:

Finished Item Number	Device Description
192110	Echo Porous Lateral Femoral Hip Stem
113626	Comprehensive Primary Mini Shoulder Stem
11-301325	Arcos Standard Hip Stem
150464	OSS Diaphyseal Segment
113604	Comprehensive Primary Micro Shoulder Stem

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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)	"Intercondular 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) standard use 0-6" calipers (b) standard use 0-1' micrometers, (b) standard use 0-2' Indicators, (b) standard use radius gage sets and (b) ball micrometers.

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Your firm was unable to provide documented justification for why actual equipment used was not documented in each of the 35 DHRs (SQ 11/18/2016).

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

OBSERVATION 11

Sampling plans are not based on valid statistical rationale.

Specifically,

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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) require (sample/mfg lot after sterilization. Review of the five largest screw DHRs revealed manufactured quantities between (b) (4) devices per lot. Your firm has distributed at least (b) (4) Lactosorb plate devices from 07/01/2014 to 10/13/2016.

ii. Finished LactoSorb screws made from (b) (4) require (sample/mfg lot after sterilization. Review of the five largest screw DHRs revealed all five lots contained (b) devices. Your firm has distributed at least (b) (4) Lactosorb devices that have been manufactured from (b) (4) from 07/01/2014 to 10/13/2016.

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 (hours while each screw produced thereafter had been exposed for subsequently less time. This operator was manufacturing a lot containing (b) devices and, according to your firm's (b) system, the minimum amount of time required to manufacture this lot would be (b) 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 12

Procedures for rework of nonconforming product have not been adequately established.

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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 (*i.e.* ( ) are not defined by procedure. He confirmed that (b) (4) are not specified. Moreover, a (b) (4) step to remove any residual (b) (4) after (b) (4) has not been defined by procedure.

B. Devices associated with 2 of 35 deviations were (b) (4) (*i.e.*, reworked) due to the presence of cosmetic defects. (b) (4) is the process of (b) (4) (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)

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(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 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 *QP0001: 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 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*

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(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.

Annotations to Observations

Observation 1:	Promised to correct
Observation 2:	Promised to correct
Observation 3:	Promised to correct
Observation 4:	Promised to correct
Observation 5:	Promised to correct
Observation 6:	Promised to correct
Observation 7:	Promised to correct
Observation 8:	Promised to correct
Observation 9:	Promised to correct
Observation 10:	Promised to correct
Observation 11:	Promised to correct
Observation 12:	Promised to correct
Observation 13:	Promised to correct
Observation 14:	Promised to correct

*DATES OF INSPECTION

9/12/2016(Mon),9/13/2016(Tue),9/14/2016(Wed),9/15/2016(Thu),9/16/2016(Fri),9/19/2016(Mon),9/22/2016(Thu),9/23/2016(Fri),9/26/2016(Mon),9/27/2016(Tue),9/28/2016(Wed),9/29/2016(Thu),9/30/2016(Fri),10/11/2016(Tue),10/12/2016(Wed),10/13/2016(Thu),10/14/2016(Fri),11/15/2016(Tue),11/16/2016(Wed),11/17/2016(Thu),11/18/2016(Fri),11/22/2016(Tue)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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11/22/2016

X Joseph R Strelnik
Joseph R Strelnik
Investigator
Signed by: Joseph R. Strelnik -S

11/22/2016

X Suyang Qin
Suyang Qin
Investigator
Signed by: Suyang Qin -S

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EMPLOYEE(S) SIGNATURE
Thomas A Peter, Investigator
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Suyang Qin, Investigator

11/22/2016
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Investigator
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DATE ISSUED
11/22/2016

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."