# Zimmer Biomet, Inc.

## Response to FDA-483 Issued on April 24, 2018


May 15, 2018

ZIMMER BIOMET
Your progress. Our promise.

56 E. Bell Drive
Warsaw, IN 46582
Tel (574) 267-6131
www.zimmerbiomet.com

**Response to Form FDA 483 Issued to Zimmer Biomet, Inc. on April 24, 2018**

May 15, 2018

***Confidential: Contains Trade Secrets and Confidential Commercial Information***

Joseph Matrisciano
Program Division Director
Office of Medical Device and Radiological Health Operations
Division 1
One Montvale Avenue
4th Floor
Stoneham, MA 02180

**Via electronic mail to oradevices1firmresponses@fda.hhs.gov**

Subject: Response to Form FDA 483 Observations Issued to Zimmer Biomet, Inc. (FEI 1825034) on April 24, 2018

Dear Mr. Matrisciano:

On April 24, 2018, Food and Drug Administration (FDA or Agency) concluded an inspection of the Zimmer Biomet, Inc. (Zimmer Biomet or the Company) facility located at 56 East Bell Drive in Warsaw, Indiana, 46582 (the Warsaw North Campus), and issued Inspectional Observations on Form FDA 483. Zimmer Biomet's initial responses to the Inspectional Observations are provided in the attached response. The inspection in April 2018 focused primarily on corrective actions addressing the FDA-483 observations from the prior Warsaw North Campus inspection that concluded in November 2016 and Zimmer Biomet's related Project Polaris remediation program.

(b) (4) Remediation Program Background

Following the 2016 FDA inspection, Zimmer Biomet initiated an extensive and systemic Quality Management System (QMS) remediation project at the Warsaw North Campus, referred to as (b) (4) included corrective actions to address not only the FDA-483 observations from the 2016 FDA inspection, but also to address findings from detailed baseline QMS audits performed by (b) (4) QMS expert auditors. This project has been—and continues to be—a top priority of Zimmer Biomet, (b) (4) .

The (b) (4) remediation plans were presented (b) (4), (b) (5), (b) (7)(A) providing detailed information on the corrective action plans and progress in the initial FDA-483 response submitted to FDA on December 21, 2016, and in updates submitted on January 17, 2017, February 17, 2017, April 25, 2017, July 31, 2017, November 17, 2017, and March 29, 2018. In the March 2018 update,

ZIMMER BIOMET
Your progress. Our promise.

Zimmer Biomet communicated that the Warsaw North Campus had completed and closed (b) (4) (b) (4) corrective and preventive actions (CAPAs) (b) (4)) addressing the 2016 FDA-483 observations and discussion points, with the remaining work planned for completion by the (b) (4) (b) (4) . Zimmer Biomet plans to submit to FDA its next full progress update addressing the 2016 FDA-483 observations on or before (b) (4) .

(b) (4), (b) (5), (b) (7)(A) , (b) (4), (b) (5), (b) (7)(A)

Over the past (b) (4) months, Zimmer Biomet has been steadily progressing (b) (4) Importantly and in accordance with the plan (b) (4) remediation work streams are still in progress. The April 2018 FDA-483 observations reflect the work-in-progress nature of (b) (4) . Zimmer Biomet believes that the Warsaw North Campus has demonstrated considerable improvement over the past year and a half. We hope those positive observations and comments are reflected in the establishment inspection report narrative. Regardless, we fully understand and appreciate that more work is required and needs to be completed to create and sustain the robust quality system we are committed to establishing.

April 2018 FDA Inspection and Patient Safety

At the conclusion of the Warsaw North Campus FDA inspection on April 24, 2018, the FDA investigators issued an FDA-483 with 11 inspectional observations. Zimmer Biomet recognizes and takes seriously the significance of the observations in the FDA-483 and has ensured that each observation requiring corrective action is associated with an active CAPA. Some CAPAs relating to the April 2018 observations were opened prior to the inspection as part of (b) (4) (b) (4) or to address previous internal audits or inspectional findings. Where such CAPAs existed, the scope of such CAPAs was updated to incorporate the recent FDA-483 observations. As a part of the ongoing multi-year remediation effort, the Company continues to work diligently with independent (b) (4) expert (b) (4) to address both existing and new FDA-483 observations.

Zimmer Biomet does not believe that any of the April 2018 FDA-483 observations identifies a specific issue or trend impacting the performance of any particular product released to the market that was not already addressed by the Zimmer Biomet QMS (b) (4) . Zimmer Biomet is committed to taking all actions necessary to ensure that its products and systems are in compliance with all FDA requirements, and the Company is steadfast in its determination that its products must be safe and effective.

During the execution of (b) (4) remediation activities, the Warsaw North Campus QMS "listening" systems and quality data trending processes are continuously monitoring for unanticipated risks and occurrences. Zimmer Biomet promptly investigates any signals identified by the QMS listening systems to evaluate and identify containment actions, assess patient safety risk, and establish and implement appropriate corrective actions. For example, during the 2018 inspection, Zimmer Biomet provided evidence to the FDA investigators showing that the Company deployed (b)(4) internal quality holds within the Warsaw North Campus during the first part of 2018 while investigating signals from the Company's QMS listening systems. (b) (4) issues identified by the QMS listening systems were escalated to product recalls, all of which were reported to FDA in accordance with 21 C.F.R. Part 806.

A significant part (both in importance and in scope) of (b) (4) is the remediation of all active design history files (DHFs) for all implants and instruments—approximately (b) (4) DHFs in total. To support continued distribution during the DHF remediation period and to confirm patient safety, Zimmer Biomet completed a Device Performance Review (DPR) assessment for each product family, in addition to the Company's standard post-market surveillance activities. The DPR process used a risk-based approach to assess whether the performance of Warsaw North Campus products is in-line with similar products in the industry. As previously reported to FDA in the progress updates for the 2016 FDA-483, the DPRs collected and analyzed publicly available information (e.g., published literature and national registries) and internal information (e.g., product complaints and CAPAs). If a DPR did not meet its pre-defined acceptance criteria, then the product was evaluated through Zimmer Biomet's Health Hazard Evaluation (HHE) process to determine whether field actions or other corrective actions should be initiated. Zimmer Biomet completed (b) (4) DPR assessments, (b)(4) of which were escalated to the HHE process for patient safety review by health care professionals and Zimmer Biomet's patient safety review committees. Two of the (b) (4) HHEs resulted in field actions, both of which were reported to FDA under 21 C.F.R. Part 806. Based on the objective data generated through the DPR assessments and on-going post-market surveillance activities, Zimmer Biomet remains confident in the performance and safety of the Warsaw North Campus devices.

Additional Information for Select Observations

During the 2018 FDA inspection, Zimmer Biomet personnel and the FDA Investigators disagreed on some technical CAPA topics (or Zimmer Biomet did not clearly provide sufficient context or explanation), as evidenced by some of the FDA-483 observations. For those areas of disagreement or misunderstanding, Zimmer Biomet has included additional detailed information and context in the attached responses to Observations 1(A), 1(B), 2, and 10 that should be taken into account. Set forth below is a brief executive summary for those observations.

*Observation 1(A)*

Observation 1(A) states that Zimmer Biomet did not implement corrective actions sufficient to prevent the recurrence of bacterial endotoxin test (BET) excursions and questions Zimmer Biomet's decision not to conduct a recall related to a BET failure. We believe that the investigators misunderstood or lacked important context about the information reviewed by Zimmer Biomet's Global Recall Committee (GRC) when it decided that that no field action was required. Specifically, the observation claims that a Zimmer Biomet study report did not provide objective evidence sufficient to support the no-field-action decision. This study, however, was not the sole, or even primary, source of data that the GRC relied upon when making its decision. Further, the observation cites deficiencies in the study, as if the study was a validation. The study, to the contrary, was not a validation; it was a characterization study for a new cleaning process.

As explained further in the attached detailed response to the FDA-483, a (b) (4) BET failure in February 2017 was identified during process monitoring. Zimmer Biomet fully investigated the BET failure, including testing all available units from the affected process monitoring time period with (b) (4) BET failures and (b) (4) results even approaching the specification limit. Based on extensive testing data and statistical analyses, Zimmer Biomet concluded that the failure was an isolated outlier without any impact on product. The GRC's consideration of the BET failure and the associated HHE was supported by this extensive data, not just the process characterization study report cited in the Observation. Reviewing all of the data in combination, the GRC reasonably and correctly determined that (b) (4) .

*Observation 1(B)*

Observation 1(B) states that Zimmer Biomet has not taken action commensurate with risk with respect to cleaning validations. The observation also states that certain cleaning processes currently in use at the Warsaw North Campus are not in a state of control, due in part to low process capability (Ppk) values. Further, the observation states that the (b) (4) (b) (4) cleaning process has not been validated. Zimmer Biomet believes that these aspects of Observation 1(B) are a byproduct of a misunderstanding between the Investigators and Zimmer Biomet personnel.

First, Zimmer Biomet has taken several actions commensurate with cleaning process validation, remediation, and monitoring risks, including initiating multiple product holds since the 2016 inspection. In fact, based on cleaning process validation results, the production of certain product families has remained on hold since the previous inspection. These product holds have been taken commensurate with product and process risk and to prevent potential risk to patients.

Second, the Ppk values cited in the observation are for an non-validated cleaning process that is operating under interim controls, including substantially increased process monitoring. Ppk values are not the method that Zimmer Biomet uses to ensure control of this non-validated process, and Ppk is generally not considered an appropriate measure for non-validated, non-normal data. Rather, Zimmer Biomet monitors non-validated processes (like the one cited in the observation) with control charts, and violations of control limits result in the initiation of, and investigation under, Issue Evaluations (IEs) and further action, including CAPAs and field actions, as warranted.

Finally, only the (b) (4) device sub-families failed the (b) (4) cleaning validation, and those products have been on both production and ship holds since the (b) (4) . For (b) (4) device sub-families, the test data was conforming and production was resumed under interim controls with increased process monitoring.

Based on the foregoing, Zimmer Biomet is confident that cleaning processes currently in use at the Warsaw North Campus are operating in a state of control, either as validated processes, or as non-validated processes subject to adequate interim controls and monitoring via control charting.

*Observation 2*

Observation 2 concerns the validation of the (b) (4) sterilization process previously used by the Warsaw North Campus, which is referred to as (b) (4) (note that (b) (4) has since been replaced by a (b) (4) ). The observation states that (b) (4) was not properly validated and that studies performed "in lieu of" revalidation are not sufficient to ensure the sterility of previously distributed product. As reported in response to Observation 1(B) from the 2016 FDA-483, and as set forth in the attached response (b) (4) was, in fact, fully validated in 2003, and thus no revalidation was or is needed. Further, (b) (4) remained in a validated state, passing all of its annual re-qualifications. In September 2016, independent sterilization experts reviewed the (b) (4) validation data and confirmed the adequacy of the validation.

The studies referenced in Observation 2 were annual re-qualification studies intended to determine the continued appropriateness of the sterilization cycle to deliver sterile products for the current Warsaw North Campus products using the cycle. The studies were not intended to serve as validations, nor were they performed in lieu of revalidation, as stated in the Observation, since revalidation was unnecessary given that (b) (4) was, and remained, validated. Even so, Zimmer Biomet believes that the requalification studies do, in fact, provide evidence of (b) (4) effectiveness in achieving a (b) (4) , as explained in the attached response. All of the foregoing supports the sterility of product in the field.

*Observation 10*

Observation 10 states that Zimmer Biomet did not adequately establish process controls for a specific packaging sealer (which has since been removed from production in accordance with a pre-inspection (b) (4) obsolescence plan) because Zimmer Biomet did not include pressure as a process control. The observation quotes the sealer's instructions manual as evidence that there are pressure control features in the sealer that Zimmer Biomet should have, but did not, use.

We respectfully disagree with this observation. The necessary process controls were established to ensure that the sealer conformed to Zimmer Biomet's established specifications. Zimmer Biomet is not required to use all available features on a piece of equipment, but it must identify, qualify, control, and monitor the critical features, and the resulting process. Prior to the specified sealer's first use, Zimmer Biomet determined that the pressure setting referred to in the observation was not a critical parameter that required independent monitoring. This determination was based on the limitations of the legacy equipment, specifically, that it did not have a feature that allowed operators to set pressure, and there was no quantitative pressure monitoring device. Further, the (b) (4) function described in the observation is only intended to verify the (b) (4) and does not provide quantitative sealing pressure for the purposes of process monitoring. These factors make use of pressure as an in-process control method unreliable and impractical.

Zimmer Biomet notes that the manufacturer of the packaging material sealed by the sealer at issue indicates that, for most heat seal materials, pressure is the least significant of the three factors required to make an adequate heat seal. This conclusion is further supported by Zimmer Biomet's extensive testing of (b) (4) (over (b) (4) process monitoring samples for this sealer alone since September 2016), which demonstrate very robust product performance from this sealer with no failures noted, despite the fact that pressure was not identified or controlled as a critical parameter. Supported by this robust data, Zimmer Biomet is

confident that its use of in-process temperature monitoring and product attribute monitoring (for seal strength and integrity) ensured the validated state of the now-obsoleted sealer and continuous product conformance to specifications.

CAPA Actions to Address 2018 FDA-483 Observations

Zimmer Biomet remains committed to complying with the requirements of the Federal Food, Drug, and Cosmetic Act and taking the actions that are necessary to address fully the Inspectional Observations listed on the FDA-483. In addition, Zimmer Biomet is committed to ensuring that its products, processes, procedures, and systems comply with FDA requirements and that its products remain safe and effective. Zimmer Biomet has CAPAs assigned to address the Inspectional Observations, as listed in Table 1 below. Only four of the FDA-483 observations required new CAPAs, while the others were addressed as part of CAPAs opened prior to the inspection as part of (b) (4) and other audit findings. In addition to correcting the specific items listed in the FDA-483, Zimmer Biomet has taken and is continuing to take actions to address systemic issues, as described in detail in the attached response.

Table 1. CAPAs Addressing FDA-483 Inspectional Observations

| OBS # | OBSERVATION DESCRIPTION | CAPA # | Containment / Correction | Investigation Root Cause Action Plan | Action Implementation | Verification of Effectiveness |
|---|---|---|---|---|---|---|
| | **Legend for Status Andon ->** | | | In Progress | Closed | Not Started |
| 1A | ZFA Documentation | 3241 | 3-Feb-17 | 16-Jul-17 | 3-Oct-17 | 11-Dec-17 |
| 1B | (b) (4) Clean Validations CAPA | 3092 | 14-Dec-16 | 14-Feb-17 | (b) (4) | |
| 1C | Design Controls | 2719 | 16-Dec-16 | 3-Jan-17 | | |
| 1D | NCR Trending | 4031 | 13-Nov-17 | (b) (4) | | |
| 1E | Single Code NCRs for Multiple Deficiencies | 4031 | 13-Nov-17 | | | |
| 2 | (b) (4) Sterilization CAPA | 2867 | 17-Dec-16 | 7-Mar-17 | 14-Nov-17 | 30-Nov-17 |
| 3 | Risk Management | 4257 | 7-Mar-18 | (b) (4) | | |
| 4 | Supplier Cleaning TMV Validations | 4509 | 10-May-18 | | | |
| 5 | Environmental Excursions | 4523 | 6-Jun-18 | | | |
| | Work Environment Practices | 4521 | 5-Jun-18 | | | |
| 6 | Consistent NCR/CCR Initiation | 4031 | 13-Nov-17 | | | |
| | Inconsistent NCR Defect Codes | 4031 | 13-Nov-17 | | | |
| 7 | Pkg Inspection Criteria | 4508 | 10-May-18 | | | |
| 8 | Training ID and Documentation | 3127 | 6-Jan-17 | 14-Jun-17 | (b) (4) | (b) (4) |
| 9 | Process Monitoring Parameter Control | 4129 | 2-Jan-18 | (b) (4) | | |
| 10 | (b) (4) Sealer Remediation CAPA | 2380 | 27-Dec-16 | 2-Feb-17 | | |
| 11 | Uncontrolled Personal Gage | 4510 | 10-May-18 | (b) (4) | | |

New CAPA

This letter and its attachments contain trade secrets and confidential commercial information not subject to disclosure under the Freedom of Information Act. Accordingly, we respectfully request that this letter and its attachments be treated as confidential. If FDA plans to release this letter, any portions of its content, or any attachments, Zimmer Biomet respectfully requests that FDA provide Zimmer Biomet an opportunity to redact all trade secrets and confidential commercial information prior to disclosure.

Zimmer Biomet respectfully requests a meeting with the FDA Division 1 Office of Medical Device and Radiological Health Operations Staff to discuss our response after FDA has completed the initial review of the information included in this response. The purpose of the meeting would be to discuss any FDA concerns or feedback and review the remaining (b) (4) actions and projected timeline.

ZIMMER BIOMET
Your progress. Our promise.

Zimmer Biomet plans to provide regular updates to this initial FDA-483 response. We anticipate providing the first update response by (b) (4) but this date is subject to change based on further dialogue with and feedback from FDA, including any discussion during the requested meeting. If you have any questions or need any clarification during your review of the attached response, please do not hesitate to contact me at jeff.gensler@zimmerbiomet.com or 574-527-2736.

Respectfully,

Jeff Gensler
Vice President, Quality Assurance and Quality Control
Zimmer Biomet

cc: Gina Bracket, Director of Compliance Brach, FDA OMDRHO Division 1

Arduino Frankovic, Director of Investigations Branch, FDA OMDRHO Division 1

Stephanie Durso, Compliance Officer, FDA OMDRHO Division 1

Bryan Hanson
President and Chief Executive Officer, Zimmer Biomet

David Kunz
Senior Vice President, Global Quality and Regulatory Affairs, Zimmer Biomet

Ken Tripp
Senior Vice President, Global Operations & Logistics, Zimmer Biomet

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 1

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 1**

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

***This is a repeat observation from the FDA inspection date 9/12/2016 to 11/22/2016.***

**Specifically,**

**FDA Observation 1(A)**

**A. Corrective actions were not effective in preventing recurrence of bacterial endotoxin test (BET) failures in polyethylene devices.**

**CAPA #CA-03241 was initiated on 1/25/2017 after two polyethylene devices cleaned in work center (b) (4) failed bacterial endotoxin testing (BET). A (b) (4) (b) (4)" in the work center was identified as the root cause of the failures and was removed from service on 1/23/2017. Your firm conducted a recall of all polyethylene product cleaned in the work center between 12/12/2016 and 1/20/2017.**

**Subsequently, another polyethylene device cleaned in work center (b) (4) on 2/27/2017 failed BET (item (b) (4) ). The third occurrence was added to CAPA #CA-03241 because "it was determined that the failure was consistent with the original failures identified". The CAPA attributed the root cause of the third failure to the manual nature of the cleaning operation and "if performed inadequately" can lead to failure to meet requirements.**

**In response to the third BET failure, HHE (Health Hazard Evaluation)/ZFA (Zimmer Field Action) #2017-109 was initiated to assess the need for additional field action. On 5/5/2017, your firm determined no field action was necessary because a study report ((b) (4) dated 4/5/2017) demonstrated the manual cleaning operation "exceeds a 99% confidence that more than 99%" of all distributed product meets specification (b) (4) EU/device). The study does not provide objective evidence to support this conclusion. Specifically:**

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

i. **The manual cleaning process involves operators (b) (4) in an (b) (4) and scrubbing them with a nylon brush. The validation of the process was found to be inadequate during the previous FDA inspection. Your firm also determined noncompliance with all four (4) OQ requirements and two (2) PQ requirements during a "Process Validation Assessment" approved on 7/24/2017.**

**To date, the process as it existed at the time has not been adequately validated. The study report ((b) (4) ) appeared to represent a performance qualification (PQ) comprising (b) (4) polyethylene device families. The study failed to demonstrate the process is consistently capable in worst-case conditions normally established during OQ (*e.g.*, (b) (4) ).**

ii. **Your firm was unable to provide objective evidence to refute the possibility that operators manually cleaned devices more rigorously during the study than would normally be performed.**

iii. **Pre-established acceptance criteria were not documented in the corresponding protocol ((b) (4) ; dated 3/22/2017) because "this is an investigative study." The study report states that cleaned devices were required to "achieve a capability of at least Ppk (b) (4)." This criterion was said to be met; however, your firm assumed the data was normally distributed. During this inspection, you re-checked the data and confirmed it was not normal and could not be transformed. As such, process capability analysis could not be performed.**

iv. **(b) (4) families of devices were tested during the study, of which two were cleaned using a (b) (4) automated machine wash. This process is not representative of the manual cleaning processes used at the time of the third BET failure.**

v. **Confidence and reliability was calculated by pooling the samples across all families tested. Recalculating the results by family yielded lower confidence and reliability than claimed in the study:**

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| Family | Confidence | Reliability |
|---|---|---|
| (b) (4) | | |

**Observation 1(A) Investigation and Response:**

Observation 1(A) concerns a bacterial endotoxin testing (BET) process monitoring failure observed on 27 Feb 2017 from a manual cleaning process for polyethylene devices that did not result in a recall or other field action. As stated in the Observation, and as described further in this response, Zimmer Biomet's Global Recall Committee (GRC) determined that there was no need to recall product associated with the reported process monitoring failure. The GRC's decision was based on the review of extensive testing and monitoring data. The Observation cites only one component of the information provided to the GRC, that is, a process characterization study report, (b) (4) "(b) (4) " (Attachment (b) (4) *, Rev 0*). As explained further below, this study was not the primary basis for the GRC's decision, and it was not a validation study, nor was it intended to be, contrary to the implication in the Observation. Zimmer Biomet stands by the GRC's original decision; no field action is warranted in connection with the February 2017 BET failure.

27 Feb 2017 BET Failure

Upon receipt of the failed BET result, Zimmer Biomet immediately took several containment and investigation steps. First, on 10 Mar 2017, Zimmer Biomet initiated Quality Hold 17-034 (Attachment 1A-B, *QH 17-034*) for all lots of finished product cleaned during the same process monitoring time period (b) (4) as the unit with the out of specification BET result ((b) (4) EU with a (b) (4) EU/device specification limit).

Second, Zimmer Biomet conducted extensive testing of other potentially affected product. Zimmer Biomet immediately submitted for BET testing all remaining untested pieces from the same production lot as the failed BET, that is, for units of part (b) (4) , production lot (b) (4) All (b) (4) BET results, (Attachment 1A-C, *BMTEP-108223_277390 BET Results*) (b) (4) (b) (4) ).

(b) (4) finished product lots were cleaned through the affected work station for the process monitoring period, (b) (4) total units. A (b) (4) lot was a component-level product that is not a finished level product. Zimmer Biomet conducted BET testing on 100% of product still under Zimmer Biomet control from those (b) (4) finished product lots, including the (b) (4) remaining

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

units from the failed device's lot and work-in-progress (WIP) and finished goods inventory. In total, (b) (4) out of the total (b) (4) total units produced were tested for BET. The BET results for the (b) (4) remaining units from the failed device lot were all below LOQ, and there were zero BET failures from the remaining product tested across the (b) (4) lots. (b) (4) of the (b) (4) units were below the limit of quantification (LOQ) and the results for the remaining (b) (4) units were all below (b) (4) EU/device, far below the specification limit of (b) (4) EU/device. The results of the additional testing, across the (b) (4) product families represented in the (b) (4) lots are as follows:

| Type | Pieces | Confidence | Reliability | BET Upper Bound |
|---|---|---|---|---|
| (b) (4) | | | | |

Based on the overwhelmingly consistent passing results for other units processed during the process monitoring period, Zimmer Biomet conducted a statistical test to determine if the 27 Feb 2017 BET failure was an outlier. A (b) (4) test for outliers confirmed that the (b) (4) EU test result is an outlier compared to other (b) (4) test results from the (b) (4) lots of finished product produced during (b) (4) on 27 Feb 2017. (Attachment 1A-D, (b) (4) _27 Feb 2017). This analysis confirms that the reported nonconformance of (b) (4) EU, was a single event that was fully contained, and the remaining population would not exhibit this event.

Finally, to further investigate the 27 Feb 2017 BET failure, Zimmer Biomet reviewed the process monitoring data from the lots from the (b) (4) part number (b) (4), production lot (b) (4) and all results were found to be conforming.

In summary, the data surrounding the 27 Feb 2017 BET failure demonstrates that the failure was an isolated outlier, as follows:

- The BET results for the (b) (4) remaining units from the failed device's lot were all below LOQ.
- For the (b) (4) lots produced during the same process monitoring period, all (b) (4) BET results were negative, with (b) (4) units below LOQ and (b) (4) units below (b) (4) EU/device, far below the specification limit of (b) (4) EU/device. In total, (b) (4) out of the total (b) (4) total units produced were tested for BET.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

- The process monitoring data from the lots from the manufacturing shift (b) (4) (b) (4) the BET failure was conforming.
- The process monitoring test results for (b) (4) units tested from 25 Jan 2017 to 10 Mar 2017 demonstrate zero failures, with the exception of failure on 27 Feb 2017.
- A (b) (4) test for outliers confirmed that the 27 Feb 2017 BET failure was an isolated event.

Following Zimmer Biomet's standard health hazard evaluation (HHE) process, HHED 03-2017-012 (Attachment 1A-E, *HHED 03-2017-012, Rev 1*) was initiated 20 Mar 2017 for the 27 Feb 2017 failure and was escalated to HHE 2017-109 (Attachment 1A-F, *HHE 2017-109, Rev 1*) on 21 Mar 2017. As part of the investigation and evaluation, Zimmer Biomet consulted with (b) (4) (b) (4)(b) (4) regarding the BET data. He concluded, with (b) (4)% confidence that the defect rate was below (b) (4)%. The lower reliability of (b) (4)% using the (b) (4) is based on the number of samples provided, not the actual reliability of the process, which can be more accurately and fully illustrated by the use of the variable data from the sampling of the lots as shown in table above, this data shows the process exceeds a six-sigma process. (b) (4) estimate of the process control using a (b) (4) (b) (4) potential on available sample size results is a very conservative estimate and should not be used to assume that (b) (4)% of the items being washed are potentially outside of the specification limits. HHE 2017-109 (Attachment 1A-F) considered this analysis and states: "(b) (4) ." This conclusion was based on BET test results for all product cleaned in (b) (4) on 27 Feb 2017 during (b) (4) shift.

The GRC's consideration of the BET failure, the associated HHE, and the data presented to the committee, resulted in a determination that no field action was warranted, as documented in the ZFA 2017-109 (Attachment 1A-H, (b) (4) *, Rev 2*) determination. Zimmer Biomet, however, acknowledges an error in (b) (4) Attachment 1A-H) regarding (b) (4) (Attachment 1A-A). Data regarding the (b) (4) cleaning process as characterized in (b) (4) (Attachment 1A-A) was included in the slides provided to the GRC. In referencing this data, ZFA 2017-109 (Attachment 1A-H) incorrectly states in the section titled Field Action Recommendation Rationale that the study demonstrates that the (b) (4) cleaning process exceeds a (b) (4) % confidence that more than (b) (4)% of distributed product is equal to or below (b) (4) EU/device. This is incorrect. The data was calculated at a (b) (4) % confidence level. However, the misinformation is inconsequential; the GRC reviewed and relied upon additional, convincing evidence, as described above. The GRC was also provided information (Attachment 1A-I, *GRC Slides for* (b) (4) )regarding (i) the testing of the remaining (b) (4) previously untested pieces from the same production lot as the BET failure, (ii) the process monitoring from the (b) (4) BET failure, and (iii) the test results from the

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

(b) (4) units (b) (4) of the population) under Zimmer Biomet's control from the (b) (4) lots processed during the same process monitoring period, all of which demonstrated that the 27 Feb 2017 was an isolated outlier event.

In addition, despite the mistake in the HHE documentation, all process monitoring test results for interim control IC-002 (Attachment 1A-J, *IC 002, Rev 10, Ultra-High Molecular Weight Polyethylene (UHMWPE) Final Cleaning*), from 25 Jan 2017 and 10 Mar 2017, demonstrate zero failures and a (b) (4)% confidence that, at least, (b) (4)% of all distributed product is within the specification limit of (b) (4) EU/device using a (b) (4) ((b) (4) (b) (4) ) for test results (including the nonconforming 27 Feb 2017 results). Additional analysis has since been performed by (b) (4) using all test values from the (b) (4) lots of finished product which demonstrates a (b) (4)% confidence that more than (b) (4)% of devices are below (b) (4) EU/Device for Vitamin E product and a (b) (4)% confidence that more than (b) (4)% of devices are below (b) (4) EU/Device for Standard Poly (Attachment 1A-K, (b) (4) ). This demonstrated performance is better than the estimated (b) (4)% confidence of (b) (4)% nonconforming documented within HHE 2017-109. Thus, the estimated occurrence rate and expected clinical outcome reviewed by the health care professional as part of ZFA 2017-109 would be unchanged. Zimmer Biomet created (b) (4) (Attachment 1A-K) to document all information contained within the slides provided to the GRC in May 2017 and revised HHE 2017-109 (Attachment 1A-F) and ZFA 2017-109 (Attachment 1A-H) to include reference to this new ZTM. The updated HHE 2017-109 (Attachment 1A-L, *HHE 2017-109, Rev 2)* and ZFA 2017-109 (Attachment 1A-M, (b) (4) *Rev 2*) were presented for a second time to the Product Safety Review Board (PSRB), surgeon review and to the Global Recall Committee (GRC), resulting in no recommended field action which reaffirms the GRC's original decision for no field action.

Cleaning Characterization Study, (b) (4)

As explained at the start of the response to this Observation, during the inspection Zimmer Biomet was not sufficiently clear when discussing (b) (4) (Attachment 1A-A) with the Investigator. As evidenced by the wording of the Observation, the Investigator assumed that the study was a performance qualification study intended to validate the (b) (4) cleaning process. This is incorrect. The study was intended to characterize, not validate, the cleaning process for polyethylene devices. Further, the study was not intended to characterize the (b) (4) cleaning process that was being used at the time of the 27 Feb 2017 BET failure. Rather, all testing and reported results within (b) (4) (Attachment 1A-A) were intended to characterize the cleaning process to be used after 10 Mar 2017, that is, the interim cleaning process using (b) (4) cleaners under interim control IC-004, Rev 12, "*Process Monitoring Of Final Cleaning*" (Attachment 1A-N, *IC 004, Rev 12, Process Monitoring*

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

*Of Final Cleaning*) and which is now captured in SOP 28.0.1, Rev 8, "*Process Monitoring Of Final Cleaning*" (Attachment 1A-O, *SOP 28.0.1, Rev 8, Process Monitoring Of Final Cleaning*), in response to findings from the 2016 FDA_483[1]. Although (b) (4) product families that were tested in the study were cleaned using the (b) (4) cleaning process, they were tested only as comparators to the (b) (4) cleaning process being characterized.

Because the Investigator misunderstood the study to be a performance qualification, he incorrectly assigned rules for validation, which requires testing for normal distribution. The Investigator requested that Zimmer Biomet convert the variable data from (b) (4) (Attachment 1A-A) to attribute data using a binomial distribution model and calculate the confidence and reliability of the process by family. This resulted in the data reproduced in Observation 1(A)(v). However, this was not an appropriate statistical treatment of the data, because variable data, by FDA's own expectations, is not to be converted to attribute data to support process validation/process capability. Further, this was a characterization study and not a validation nor was it validation data. In response to Observation 1(A), Zimmer Biomet requested (b) (4) to perform additional data analysis using all original test results from (b) (4) (Attachment 1A-A). This analysis reveals that the cleaning results demonstrated in (b) (4) (Attachment 1A-A) for all (b) (4) product families passed the bacterial endotoxin requirements of (b) (4) EU/device with a high confidence ((b) (4)%) and high reliability, with lowest reliability being (b) (4)% for the (b) (4) ) product family. The remaining (b) (4) product families had (b) (4)% reliability and above (Attachment 1A-P, *ZTR_BI_0015_17, Rev 1*).

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 1A-1 | Created Zimmer Technical Memo (ZTM) (b) (4) to include information documented within the GRC slides regarding the additional BET testing and investigation performed after the reported 27 Feb 2018 BET failure and to document the retrospective analysis showing process performance leading up to 10 Mar 2017 process improvements. (Attachment 1A-K) | 10 May 2018 |
| 1A-2 | Revised (b) (4) _17 to document that it was not intended | 11 May 2018 |

[1] Please note that the use of (b) (4) cleaners and (b) (4) was implemented as an interim in-process clean while Zimmer Biomet acquired and validated a (b) (4) Cleaning Process. Reference Observation 1(B) response for further information.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| | | |
|---|---|---|
| | to be a performance qualification study and to revise the (b)(4)% confidence to (b)(4)% confidence level and to include additional analysis by (b) (4) as stated above. (Attachment 1A-P) | |
| 1A-3 | Revised HHE 2017-109 to reference (b) (4) which documents (b)(4)% confidence more than (b) (4)% are below (b)(4) EU/Device for Vitamin E product and a (b)(4)% confidence more than (b) (4)% are below (b) (4) EU/Device for Standard Poly. (Attachment 1A-L) | 15 May 2018 |
| 1A-4 | Revised (b) (4) regarding (b) (4) and to reference (b) (4) in Item 1A-3 above and to revise section titled Field Action Recommendation Rationale from (b)(4)% confidence to (b)(4)% confidence level. (Attachment 1A-M) | 15 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| N/A | Zimmer Biomet considers this Observation closed and does not anticipate any further actions | N/A |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 1(B)**

**A. Your firm's CAPA CA-3092, opened on 12/01/2016 and in action implementation phase, is not taking action commensurate with risk. CA-3092 was opened to address inadequate "process control procedures for in-process and final cleaning" and the remediation of cleaning validations. Your Engineering Manager stated this CAPA also includes any issues that may arise from the cleaning process validations.**

**For final cleaning processes that have yet to be validated, your firm is performing additional monitoring in accordance with SOP 28.0.1, "Process Monitoring of Final Cleaning," Revision 9. These values are then interpreted in accordance with the QM 28.0, "Process Monitoring of Validated Processes," Revision 12. Additionally, the process performance indicator (Ppk) is (b) (4) for input into CAPA, though this process is not currently outlined in one of your procedures, according to your Corporate Quality Director on 04/24/2018.**

**These Ppks indicate not all of your cleaning processes are currently in control. For example, your (b) (4) ) machining group has a calculated Ppk of (b) (4) and (b) (4) for the (b) (4) ) residual testing from 01/28/2018 to 03/30/2018 and 12/16/2017 to 03/20/2018 respectively, which equates to a potential product percent defect of (b) (4) % and (b) (4) %. Additionally, your (b) (4) machining group has failed two validations: OQPQ-11047-001 r0 on 01/16/2017, and VP-11047-001 r1 on 02/22/2017 and has not yet been validated. Your firm currently manufactures and distributes products that are part of this product family.**

**Your Engineering Manager stated high results in your cleaning process monitoring data and validation testing for (b) (4) ) and (b) (4) ) extract is attributed to high levels of debris, due to the method of your firm's contracted testing. Your Engineering Manager also stated the cause of the debris had been determined to be the (b) (4) from your firm's (b) (4) and that process is required to be remediated, before the final cleaning process can be validated. However, your Engineering Manager stated the remediation to your firm's (b) (4) process is still in investigational phase and does not currently have a defined action plan under CAPA CA-3092. The debris from your (b) (4) process was first identified as the cause of particulates on your product in October 2016, as part of the retrospective testing completed under CAPA CA-02936, in Attachment 14.**

**Observation 1(B) Investigation and Response:**

Zimmer Biomet opened CAPA CA-03092 on 01 Dec 2016 to address findings from Observations 1(E) through (H) and 6(B) of the 2016 FDA-483 regarding cleaning validation and process control of in-process and final cleaning. Under CA-03092, all cleaning processes that are not subject to remediated process validations are subjected to increased process monitoring under SOP 28.0.1, "Process Monitoring of Final Cleaning" (Attachment 1B-A, *SOP 28.0.1, Rev 9, Process*

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

*Monitoring of Final Cleaning*). This is accurately reflected in Observation 1(B). However, several aspects of the Observation do not fully reflect the Warsaw North Campus's cleaning processes and monitoring.

First, the Observation states that Zimmer Biomet is not taking action commensurate with risk. This is inaccurate, as Zimmer Biomet has issued several product holds related to cleaning validation remediation and process monitoring since the 2016 inspection, (b) (4) . These product holds have been taken commensurate with product and process risk and to prevent risk to patients. Second, the Observation also asserts that some of the Warsaw North Campus cleaning processes are not in control, by virtue of low process capability (Ppk) values. However, Ppk values for the non-validated processes are not the method by which Zimmer Biomet ensures control of the process, and are not a required element of our process monitoring for the non-validated processes operating under interim process controls, as explained more fully below. Rather, the processes are monitored with control charts, and violations of control limits result in the initiation of Issue Evaluations (IEs) and further action, including CAPAs and field actions, as warranted. Finally, the Observation states that the (b) (4) machining group has not been validated. However, only the (b) (4) device sub-families failed the validation and those products have been on both production and ship holds since (b) (4) . For (b) (4) sub-families, the test data was conforming and production was resumed after the initiation of interim controls.

<u>Cleaning Process Monitoring for (b) (4) Products</u>

Prior to the recent inspection, on 03 Feb 2017, Zimmer Biomet determined from retrospective studies and the validation referenced in the Observation (i.e., OQPQ-11047-001/VP-11047-001) that certain (b) (4) products could not consistently be cleaned by the existing cleaning process. The (b) (4) parts failed the validation testing, specifically, parts with a (b) (4) surface area of (b) (4) or greater. The parts demonstrating conforming data were (b) (4) in area than those that failed the validation. All (b) (4) product was placed on Quality Hold QH-068-01, (Attachment 1B-B, *QH-071-31, QH-068 has transitioned to QH-071*), on 12 Oct 2016. Production for these higher-risk products (b) (4) . Zimmer Biomet thus took prompt and lasting risk-based action as a result of the cleaning process remediation efforts.

For cleaning of (b) (4) products after their removal from QH-068-01, Zimmer Biomet has strong process monitoring data indicating the cleaning remains in a state of control. (b) (4) For these reasons, (b) (4) serve as one of the monitoring groups for (b) (4) monitored under SOP 28.0.11,

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

"(b) (4)" (Attachment 1B-C, *SOP 28.0.11, Rev 4,* (b) (4)) Group 1: (b) (4) Parts. There have been no control limit excursions since 12 Jul 2017.

| Interim Control | Monitoring Group | Start Date | Subgroups | Control Chart Alarms | Non Conformance |
|---|---|---|---|---|---|
| (b) (4) | | | | | |

Zimmer Biomet monitors the cleaning process using control charting of the laboratory test results for product subject to increased process monitoring under Interim Controls, including SOP 28.0.1 "Process Monitoring of Final Cleaning". Every excursion beyond the pre-set control limits results in the initiation of a new Issue Evaluation (IE). The IE drives initial containment and corrective actions and is elevated to CAPA as per procedures CP07000, (Attachment 1B-D, *CP07000, Rev 4*, *Corrective and Preventative Action*), and CP07001, (Attachment 1B-E, *CP07001, Rev 4, Issue Evaluation*).

A small subset of product was isolated into a new process monitoring group when the products were identified as having differences in the manufacturing process (as explained in the next section). Process monitoring for the new group, (b) (4) machined product ("Group (b) (4)"), detected residue and Zimmer Biomet initiated a series of IEs to determine the root cause and corrective action, which is explained further below in the next section/heading. For each of the process monitoring action limit excursions for Group (b) (4) Zimmer Biomet initiated an IE; a total of (b) (4) IEs for process monitoring excursions have been opened since Group (b) (4) product was segregated from other (b) (4) families. As shown in the table below, the IEs resulted in (b) (4) holds, (b) (4) HHEDs, and (b) (4) HHEs.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| | Description | Date | Product / Quality Hold | HHED | HHE |
|---|---|---|---|---|---|
| (b) (4) | | | | | |

Ppk Values Cited in the Observation

Zimmer Biomet would like to provide additional explanation regarding the Ppk values of (b) (4) and (b) (4) for (b) (4) testing identified in the Observation. As mentioned above, Group (b) (4) (b) (4) failed process monitoring testing. As an outcome of the investigation of the IEs for the excursions, which revealed (b) (4), on 28 Feb 2018, Zimmer Biomet changed the manufacturing process flow for (b) (4) (b) (4) (b) (4) Specifically, Zimmer Biomet added (b) (4) after the (b) (4) (b) (4) (Attachment 1B-F, *ZTR_BI_0011_17*) after the (b) (4) (Attachment 1B-G, (b) (4)).

The process flow change for (b) (4) product described above was implemented in response to a process issue identified during investigation. To systematically address the issue, Zimmer Biomet opened CAPA CA-04460 on 19 Apr 2018. CAPA CA-04460 evaluates and addresses Zimmer Biomet's finding that (b) (4)

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

(b) (4) impacted Zimmer Biomet's cleaning process. CA-04460 is currently in the Correction phase and is due to be promoted to the Investigation / Root Cause phase by (b) (4). Zimmer Biomet expects that the CAPA will include a review of (b) (4) that perform manufacturing steps for Zimmer Biomet. Zimmer Biomet will include details regarding any corrective actions planned as a result of the CA-04460 investigation in future updates to this response.

The Group (b) (4) (b) (4) failures account for the (b) (4) Ppk values identified in the Observation. The raw data and Ppk values presented during the April 2018 FDA inspection did not differentiate between the new and old versions of the manufacturing process flow. The lack of granularity in the data overstated the variation for this monitoring group leading to a (b) (4) Ppk value being presented to the auditor.

Zimmer Biomet continues to react to, and take action commensurate with, risk signals from (b) (4) cleaning process monitoring. These actions, and the increased monitoring, further demonstrate Zimmer Biomet's risk-based approach to monitoring the cleaning process during ongoing remediation and also demonstrate Zimmer Biomet's control over the process.

As explained above, Zimmer Biomet does not use Ppk to assess the control of non-validated cleaning processes subject to interim controls. Rather, control charting is used to monitor the processes and to determine when further action is needed. Zimmer Biomet does calculate Ppk values for non-validated cleaning processes and the values are provided in CAPA trend and management review meetings. The Ppks are used for informational purposes only and for consistency with the reporting and review for validated cleaning processes, for which Ppk calculation and review is required by Zimmer Biomet procedures.

Zimmer Biomet segregated the new Group (b) (4) monitoring data to include only (b) (4) process challenge devices since the current process restart date of 28 Feb 2018. The table below shows that product currently being manufactured is in a controlled state, via our process control chart monitoring. Again, Ppk calculation for processes that have not been validated and have not been shown to be under normal distribution is not an appropriate statistical analysis. Ppk values are calculated and reviewed for informational purposes only and are not required under Zimmer Biomet procedures for monitoring of non-validated processes, contrary to the implication in the Observation. See the summary table below for current performance of Group (b) (4) process monitoring:

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# (b) (4)

(b) (4) Debris on (b) (4) Product

Zimmer Biomet's initial investigation into (b) (4) debris on (b) (4) product suggested a two-pronged approach to prevent the potential impingement of (b) (4) into the (b) (4) (b) (4) (1) prevention of the initial impingement and (2) greater cleaning power. To prevent or lessen the impingement, Zimmer Biomet implemented work instruction improvements to control pressures on the (b) (4) process WEQP045, Rev 3, "(b) (4) " (Attachment 1B-H, *WEQP045, Rev 3,* (b) (4) ) and trained personnel to the revisions (Attachment 1B-I, *Training Records for WEQP045*). Zimmer Biomet is exploring additional solutions including more effective (b) (4) of difficult to clean surfaces and/or switching the (b) (4) to a (b) (4) to allow easier removal in (b) (4) washing. The order of manufacturing operations for (b) (4) product is also being reviewed to minimize the amount of (b) (4) required after the (b) (4) has been applied to the device. Zimmer Biomet has installed more powerful, (b) (4) reviewed by the auditors during the inspection. Additional assets are planned for purchase to improve the cleaning process for (b) (4) applications. The new (b) (4) cleaning lines will control, monitor, and alarm on process parameters to ensure the devices receive the appropriate wash parameters, and any deviation in the parameters will result in containment and an NCR for disposition. Ultimately, the appropriate solution for individual device families will be dependent on the type of (b) (4) used, geometry of the device including difficult to clean features, and surface coatings or treatments. For example (b) (4) .

The (b) (4) is a broad spectrum test utilizing a (b) (4) from the test samples. The solvent is intended to extract oils, greases or other petroleum-based residuals. In this case, the same residue (b) (4) ) is being extracted in (b) (4) cleaning tests. The (b) (4) has the lowest permitted residue limit and is therefore the most sensitive test to

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

signal a monitoring alarm for the (b) (4). Further discussion of the Test Methods can be found in Observation 4.

Process Monitoring Excursion Due to (b) (4) Process

Finally, while investigating a process monitoring excursion under IE-04805, Zimmer Biomet identified an environmental controls and monitoring issue at an (b) (4) that may have (b) (4) product processed for Zimmer Biomet, and that the issue may have been a cause of a process monitoring bacterial endotoxin (BET) excursion observed in February 2018. To address this finding, Zimmer Biomet opened CAPA CA-04528 on 09 May 2018 to evaluate and address this finding that (b) (4) impact Zimmer Biomet cleaning and upgrade validations. CA-04528 is currently in the Correction phase and is due to be promoted to the Investigation / Root Cause phase by (b) (4) (b) (4). Zimmer Biomet will include details regarding any corrective actions planned as a result of the CA-04528 investigation in future updates to this response.

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 1B-1 | Revised work instruction WEQP045 to prevent or lessen impingement by (b) (4) by controlling pressures on the (b) (4) process (Attachment 1B-H) | 11 Jul 2017 |
| 1B-2 | Trained personnel to the revisions to WEQP045 (Attachment 1B-I).<br>• Initial training completed on revision 1<br>• Additional trained to date | 11 Aug 2017<br>14 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| N/A | Zimmer Biomet considers this Observation closed and does not anticipate any further actions | N/A |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 1**

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

***This is a repeat observation from the FDA inspection date 9/12/2016 to 11/22/2016.***

**Specifically,**

**FDA Observation 1(C)**

A. **CAPA 02719 (assigned a risk score of (b) (4) ), opened in July, 2016, identifies the need to remediate Design History Files (DHF's) as design control issues such as ambiguous design inputs, verification not demonstrating design outputs met design inputs, design transfer and inadequate statistical I techniques for V & V activities which were identified though third party audits and FDA inspections and to obsolete DHFs for other devices. As part of this CAPA, you performed a DPR (device performance review) for all DHFs to determine if any actions need to be taken (such as recall) for devices which have been and are currently being distributed.**

**These "DPR" evaluations were conducted us 1) review of national registries; 2) literature reviews and 3) occurrence rates of revision surgeries associated with serious adverse events. Since your DPR evaluation only uses on subset of complaints/MDRs (revision surgery) you have not demonstrated that you have taken a plenary "risk based" approach to evaluating products that have been and are still being distributed. Other high risk failure modes (which could result in an MDR) such as; pain, implant not assembling with mating implant, limited range of motion or fracture, have not been included in your DPR evaluations.**

**A data sort using the previous 6 months of MDR data (October 1, 2017-April 17, 2018) for implants associated with "functional performance", found the highest occurrence rates were from the "Comprehensive Reverse" product line, which is part of the extremities segment of devices. A review of the DHF (comprehensive shoulder implant) for the XL-115363, which appears to be "high" risk based on MDR events, has not yet been fully remediated, found the following;**

i. **Your input-output risk table has not been updated with potential severity levels associated with hazards. For instance hazard line (b) (4) for inadequate packaging leading to infection is assigned a severity score of (b) (4) equating to "Necessitates minor medical intervention" in your Risk Management**

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Procedure QM 4.4, Rev 13. This assigned severity level does not include the potential severity outcomes of serious injury or death which can occur as a result of infection.**

ii. **On 4/20/2018, your Director of Engineering Services stated that your occurrence scores on your input-output risk table are not currently reflective of similar family types, which is planned as part of your remediation effort. Therefore, it is unknown if residual risk levels are currently acceptable.**

iii. **Not all feedback from design validation was considered prior to releasing the product. One of the surgeons used for design validation wanted to make sure the (b) (4) works with (b) (4) . This was not addressed during the design project.**

iv. **You have no documented statistical rational for verification or validation activities. For example, you used only (b) (4) surgeons for design validation and (b) ( samples for testing design inputs 4.1 and 4.3 regarding torsion and shear testing.**

v. **Design verification did not document all test conditions for design inputs 4.1 and 4.3. Load rates (lbs/sec), defined in the protocols were not documented in any of the (b) (4 test reports.**

vi. **Design verification testing did not demonstrate your design input was met for design input 4.3. Your specification for maximum allowable motion for the glenosphere baseplate of (b) (4) inches after load showed a result of (b) (4) inches which was accepted as the "mean" testing for the part was (b) (4) inches (still out of specification). Additionally, part (b) (4) was missing test results.**

vii. ***Design inputs in your input-output risk table are ambiguous. For example, input 2.2; Range of Motion results meeting surgeon expectations. A comparison of your design inputs records which have been "remediated" show (b) (4) inputs have been updated from your input-output risk table. It is currently unknown if the current level of verification or validation for these inputs will require new or additional testing.**

viii. ***Not all design inputs have been established. Your design input records which have been remediated show (b) (4) design inputs which are missing from your**

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**input-output risk table. It is currently unknown if these design inputs have undergone verification or validation activities or if this testing may be covered under a different design project.**

***The "remediated" design inputs for this device became effective 4/9/18 during this inspection include new inputs and address inputs which were ambiguous. The remaining design stages (for example; verification testing, validation and risk management) have not yet been remediated in this DHF.**

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

In March 2016, at Zimmer Biomet's request (b) (4) audited Warsaw North Campus's design controls system and identified numerous issues. This design controls audit report was submitted to FDA with the initial update to the November 22, 2016 FDA-483. In response to the internal audit, on 19 Jul 2016, Zimmer Biomet initiated CAPA CA-02719 to investigate and assess potential gaps in design history files (DHFs) for Warsaw North Campus devices. After the completion of the previous FDA inspection in November 2016, Zimmer Biomet determined that the design control issues identified in Observation 4 of the FDA-483 issued after that inspection were within the scope of existing CA-02719. Following the recent April 2018 FDA inspection, Zimmer Biomet further determined that the design control issues identified within Observation 1(C) are also within the scope of CA-02719 as the findings relate directly to activity performed and to be performed under existing CA-02719. CAPA CA-02719 is in the Action Implementation Phase, with an anticipated end date of (b) (4). The Verification of Effectiveness Phase is currently anticipated to end (b) (4). (Attachment 1C-A, CAPA CA-02719, *Summary*)

In addition, in January 2018 and prior to the recent FDA inspection, Zimmer Biomet opened CAPA CA-04257 (Attachment 1C-B, CAPA CA-04257, *Summary*) to update risk management files. CAPA CA-04257 has been linked to CAPA CA-02719 so that the risk activities already included in CA-02719 can address the concerns raised by CA-04257. CAPA CA-04257 is in the Root Cause Action Plan phase and is expected to promote to the Action Implementation phase on (b) (4) (b) (4)

Observation 1(C) addresses two related issues: (1) the DHF remediation currently underway under the Warsaw North Campus's (b) (4) and (2) the Device Performance Reviews (DPRs) developed by Zimmer Biomet to assess whether devices are suitable for continued distribution while DHF remediation work remained on-going. This response will address each aspect of the Observation in turn.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Device Performance Reviews

During the (b) (4) DHF Remediation, Zimmer Biomet used a risk-based approach to assess whether Warsaw North Campus products are performing in-line with similar products in the industry by conducting Device Performance Reviews (DPRs). As previously reported to FDA, the DPRs collected and examined publicly available information, such as published literature and national registries, and internal information, such as product complaints and CAPAs. DPRs were assigned pre-defined acceptance criteria and if the DPR did not meet the acceptance criteria, the product was evaluated through the Zimmer Biomet Health Hazard Evaluation (HHE) process for consideration of field actions or other corrective actions. Zimmer Biomet submitted the DPR Protocol to FDA in July 2017 with the Fourth Update Response to Observation #4 of the November 2016 FDA-483 and submitted (b) (4) examples of completed DPR reports in November 2017 with the Fifth Update Response to Observation #4 of the November 2016 FDA-483. One of the (b) (4) examples was from the (b) (4) product family in the (b) (4) product segment, which is the same family of devices reviewed by the FDA investigator (and cited in the Observation) in regard to their Design History File contents during the April 2018 inspection.

The DPR process resulted in (b) (4) DPR reports covering all Warsaw North product families in the scope of the (b) (4) DHF workstream, regardless of whether the products' DHFs were planned for remediation or for rationalization through a sell-to-depletion approach. Of those (b) (4) DPR reports, (b) (4) resulted in Issue Evaluations (IEs), an input into the CAPA system. Of those (b) (4) IEs, (b) (4) resulted in HHEs. And of those (b) (4) HHEs, (b) (4) resulted in field actions, (b) (4) of which were reported to FDA under 21 C.F.R. Part 806 and provided as attachments in March 2018 with the Sixth Update Response to the 2016 FDA-483. Through this DPR process, Zimmer Biomet completed a risk-based analysis of product performance and took action as appropriate to ensure patient safety during the DHF remediation effort. All of this activity was completed prior to the recent inspection.

As identified in the present Observation, the DPR protocol instructed teams to use "revision" complaints to determine the complaint rate for comparison against the protocol's acceptance criteria. "Revision" is a surgical procedure that removes the original implant(s) after the patient has experienced a negative outcome. Revision surgery represents the end of the implant's useful life and the revision rate of a device family can be considered the inverse of the survival rate, which is often cited in clinical literature or national registries.

Zimmer Biomet acknowledges that there are other types of complaints short of revision surgery that may impact patient safety and that may be reported as MDRs. However, Zimmer Biomet

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

believes that revision complaints are the right choice to serve as the signal complaints for several reasons:

- The United Kingdom's National Institute for Health and Care Excellence (NICE) has published acceptance criteria for the revision of orthopedic implants that are commonly relied upon within the orthopedic industry (Technology appraisal guidance TA304, published 26 Feb 2014 by NICE, developed by the Orthopaedic Data Evaluation Panel (ODEP)). The guideline is a 1% overall revision rate (i.e., 99% survivability) within a cohort of devices for each year its life. For example, within a cohort of devices that have been in use for over 10 years, a survivability rate of 90% or higher (i.e., revision rate of 10% or lower) is considered to be acceptable.
- We note that revisions reported in national registries are not limited to those revisions stemming from an assignable cause to the device itself and could be related to patient- or surgeon-related factors separate from the device. The DPRs were structured to similarly consider all reported revision complaints, even when the revision was not traceable to a specific product deficiency.
- Revision surgeries are typically a treatment of last resort for patients and surgeons and are usually performed to address significant adverse events experienced by the patient. It is highly unlikely that a surgeon would perform a revision surgery if the patient was not experiencing one or more significant adverse events, including those listed in the Observation—pain, limited range of motion, and fracture. Thus, DPR reports, which were conducted using revision complaints, inherently include other adverse events experienced by patients that progressed into the higher severity event of revision surgery. To confirm this concept, Zimmer Biomet is reviewing the most severe harms assigned to design inputs for representative products reviewed under the DPR process to determine whether there are design inputs that were assigned (b) (4) . This review will confirm whether, by considering revision surgery in the DPR reviews, Zimmer Biomet accounted for the (b) (4) for critical design inputs.

Based on the foregoing, Zimmer Biomet stands behind its completed DPRs as an acceptable risk-based approach to assess whether Warsaw North Campus products are performing in line with similar products in the industry and does not intend to make any revisions to the DPR files.

DHF Remediation

As identified in the Observation, Zimmer Biomet is in the midst of a (b) (4) DHF remediation project for Warsaw North Campus medical devices under (b) (4) DHF workstream was designed to progress all DHFs that are not scheduled for rationalization through a series of four stages. Zimmer Biomet's intent for the remediation plan has always

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

been to complete each stage for all DHFs before progressing any one DHF to the end. The DPRs, discussed above, provide the justification for this step-wise approach.

The (b) (4) DHF remediation work is divided into four stages, each of which includes formal Design Reviews. Stage 1 reviews and remediates (b) (4), Stage 2 reviews and remediates (b) (4), Stage 3 reviews and remediates (b) (4) and Stage 4 reviews and remediates final reports for (b) (4), with additional documents spread throughout the four stages. Table 1 shows an overview of the Stages and a snapshot of current status. The project is expected to be completed by the (b) (4).

| Table 1 - CAPA CA-02719 (b) (4) DHF Remediation - Staged Approach | | | |
|---|---|---|---|
| **Stage 1** | **Stage 2** | **Stage 3** | **Stage 4** |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) |
| (b) (4) | (b) (4) | (b) (4) | (b) (4) |

Although the DHFs are progressing through the stages as a group, rather than individual DHFs progressing through all four stages sequentially, remediation work nevertheless is occurring across multiple stages at once. For example, according to the protocol, much of the remediation in Stage 3 includes tasks with long lead times, such as physical testing of devices, so that waiting to begin Stage 3 work until Stages 1 and 2 are complete would necessarily extend the overall project timeframe. Therefore, some Stage 3 remediation tasks that do not rely on remediation of the Risk Analyses in Stage 2 occur at an earlier time. These Stage 3 tasks include the evaluation of existing Test Reports and their suitability as Design Verification evidence.

The remediation work is being authored, approved, and archived within (b) (4), a software tool branded in Zimmer Biomet as the (b) (4)" This software allows content to be created in a library that can be applied to multiple DHFs, ensuring that like devices are treated in a standardized way. Because of the nature of the (b) (4) DHF remediation work described herein, it has always been the plan to complete DHFs concurrently throughout the project as opposed to one DHF at a time. This process allows for the highest quality DHFs, completed in the shortest possible time, using a software tool that promotes consistency and sharing of content wherever appropriate. The staged DHF remediation approach for this effort is consistent with the approach used for the remediation of (b) (4) instrument DHF files at Warsaw

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

West (i.e., Observation 8 from the Warsaw West 2015 FDA Inspection, which completed in June 2017).

Under the (b) (4) DHF remediation protocol, Zimmer Biomet teams assess whether any actions with respect to product in the field or product in production are needed via certain triggers, such as the failure of Design Verification for any new or revised Design Inputs. In response to the findings in Observation 1(C), Zimmer Biomet will now conduct such impact assessments throughout the (b) (4) DHF remediation process by adding impact assessments to the already scheduled Design Reviews. Specifically, the Stage 2 Design Review will be updated to include an impact assessment for any newly created or remediated (b) (4), documented in the meeting minutes. This assessment will evaluate whether the current (b) (4) evidence, even in draft remediated form, supports that the (b) (4) will satisfy the (b) (4).

DHF Remediation Examples in Observation 1(C)

Observation 1(C)(i) asserts that the severity levels associated with hazards do not include all potential severity outcomes. The input-output risk table in the DHF for product (b) (4) which is the source of the finding, has not yet been remediated with regard to Risk Analysis. However, to ensure that severity levels are associated with all potential severity outcomes, Zimmer Biomet revised the (b) (4) Risk Management protocols governing dFMEA and uFMEA to include an instruction that all potential severity levels relevant for that device be included and Zimmer Biomet is in the process of training personnel to the revisions (Attachment 1C-C, *Product Characterization/Design Failure Mode Effect Analysis (DFMEA)/ Risk Control Trace Matrix (RCTM) for Design History Files within* (b) (4) and Attachment 1C-D, *Risk Management Plan (RMP)/ Use Failure Mode Effect Analysis (UFMEA) for Design History Files within* (b) (4)). Zimmer Biomet also intends to make corresponding revisions to the corporate procedures for Risk Management, which include CP03030 Hazard Analysis Rev 1 and CP03040 Failure Modes and Effects Analysis Rev 2.

Observation 1(C)(ii) asserts that occurrence scores within the Risk Analysis are not reflective of similar family types. As stated above, although the User Needs and Design Inputs have been remediated and included in new DHF documents, the input-output risk table for the DHF cited in the Observation has not yet been remediated with regard to Risk Analysis. Ensuring that remediated occurrence scores are reflective of similar family types is already a planned action within the (b) (4) DHF remediation project, facilitated by the (b) (4) software which allows the curation of content in a library that is applied to each DHF which requires it.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Observations 1(C)(iii) through (vi) identify several gaps in the Design Verification and Validation documentation for the DHF for product (b) (4) . Each of these gaps are previously recognized deficiencies in the legacy DHF documentation and all are being addressed by CAPA CA-02719 and/or CAPA CA-04257 and the (b) (4) DHF remediation activity. The DHF cited in the Observation has not yet completed Design Validation or Verification remediation activity.

Observations 1(C)(vii) and (viii) identify deficiencies in the pre-remediation Design Inputs, both that the inputs were ambiguous and that not all inputs had been established. Both of these gaps are previously recognized deficiencies in the legacy DHF documentation that are being addressed by CAPA CA-02719 and the (b) (4) DHF remediation activity. As acknowledged in the Observation, the Design Inputs for the DHF for product (b) (4) have been remediated under (b) (4) to include the previously missing inputs and to clarify the previously ambiguous inputs. These remediated Design Inputs were provided during the inspection and the FDA-483 does not contain any observations in regard to the remediated inputs' adequacy. Further, as described above, Zimmer Biomet has now incorporated an impact assessment into the (b) (4) DHF Design Review process to evaluate any potential patient safety impact of new or updated Design Inputs (Attachment 1C-E, *Design Reviews for* (b) (4) *Design Control and Risk Management Remediation*).

For the DHF identified in the Observation, Zimmer Biomet conducted an impact assessment on the (b) (4) new and (b) (4) updated Design Inputs that were included in the Observation (Attachment 1C-F, *Impact Assessment of New and Updated Design Inputs for Comprehensive Reverse*). The impact assessment determined that the new and updated Design Inputs did not result in any previously unrecognized or unmitigated risks. Design Verification work occurring throughout the project was sufficient to provide assurance that the Design Outputs will meet the new and updated Design Inputs. In one case, the Design Verification remediation process had already triggered an Issue Evaluation (IE) per the existing (b) (4) protocols to analyze the potential patient safety impact of a particular gap. This impact assessment serves as a prototype of the same process that will now be conducted within the (b) (4) remediation process, in addition to the triggers that are already built into the process for the assessment of patient safety impact.

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 1C-1 | Revised the appropriate (b) (4) Risk Management protocols to include an instruction that all potential severity levels relevant for that device be included (Attachments 1C-C and 1C-D) | 10 May 2018 |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| | | |
|---|---|---|
| 1C-2 | Revised the appropriate (b) (4) DHF Remediation protocol to require impact assessments as part of the Stage 2, 3, and 4 Design Reviews (Attachment 1C-E) | 10 May 2018 |
| 1C-3 | Conducted an impact assessment for the (b) (4) new and (b) (4) updated Design Inputs for the DHF for product (b) (4) and determined that there were no previously unrecognized or unmitigated risks (Attachment 1C-F) | 10 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 1C-4 | Conduct training to the revised (b) (4) Design Control and Risk Management protocols | (b) (4) |
| 1C-5 | Review the (b) (4) assigned to Design Inputs for representative products reviewed under the DPR process to confirm whether (b) (4) | (b) (4) |
| 1C-6 | Revise CP03030 Hazard Analysis Rev 1 and CP03040 Failure Modes and Effects Analysis Rev 2 to include an instruction that all potential severity levels relevant for that device be included | (b) (4) |
| 1C-7 | CAPA CA-02719 Action Implementation Phase Complete | (b) (4) |
| 1C-8 | CAPA CA-02719 VOE Phase Complete | (b) (4) |
| 1C-9 | CAPA CA-04257 Root Cause Action Plan Phase Complete | (b) (4) |
| 1C-10 | CAPA CA-04257 Action Implementation Phase Complete | To be provided in a future response |
| 1C-11 | CAPA CA-04257 VOE Phase Complete | To be provided in a future response |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 1(D)**

A. ***WI070002: NCR Quality Trending*** **(Rev. 1) instructs to** (b) (4) **. However, on 4/17/2018, your firm's Interim VP of QA/RC and Engineer Manager confirmed that common cause rework (CCR) data has never been reviewed as a quality data source. CCRs are intended to document corrections and rework for "cosmetic" nonconformities.**

**Observation 1(D) Investigation and Response:**

On 02 Nov 2017, prior to the recent inspection, Zimmer Biomet initiated CAPA CA-04031 (Attachment 1D-A, CAPA CA-04031, *Summary*) to improve the non-conforming product process at the Warsaw North Campus. After the inspection, Zimmer Biomet revised the scope of CA-04031 to include the findings from Observations 1(D), 1(E), and 6. CA-04031 is currently in the Root Cause / Action Plan Phase and is due to be promoted to the Action Implementation Phase by (b) (4)

Under the Warsaw North Campus non-conforming product process, non-conformances identified during the manufacturing process are categorized as either common cause (CCR records in the (b) (4) system) or special cause (NCR records in the (b) (4) sytem). Implementation of the CCR category began in mid-September 2017 with the release of QM 13.1 Rev 5, "Control of Nonconforming Product" (Attachment 1D-B, *QM 13.1, Rev 5*, *Control of Nonconforming Product*), and SOP 13.1.1 Rev 3, "Nonconforming Product Procedure" (Attachment 1D-C, *SOP 13.1.1, Rev 3, Nonconforming Product Procedure*). CCRs are intended to be used for any identified product abnormality that has been deemed inherent to the manufacturing process and can be reworked, and not simply for cosmetic nonconformities, as stated in the Observation.

Contrary to the reported statement in the Observation that CCR data has "never" been reviewed as a quality data source, trending of CCRs is required by SOP 14.0.18 Rev 7, "CAPA Trend Review Work Instruction" (Attachment 1D-D, *SOP 14.0.18, Rev 7, CAPA Trend Review Work Instruction*), and INST 14.0.18.3 Rev 1, "Nonconformance Report Trending" (Attachment 1D-E, *INST 14.0.18.3, Rev 1, Nonconformance Report Trending*). Review of CCR trends during (b) (4) CAPA trends meetings began in October of 2017 and continued for (b) (4) (b) (4) (Attachment 1D-F, *October-December 2017 North Campus CAPA Trend Review Slides)*. After trending requirements were updated in January 2018 under harmonized procedures SOP 070001 Rev 1, "Quality System Trend Review" (Attachment 1D-G, *SOP 070001, Rev 1, Quality*

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

*System Trend Review*), and WI 070002 Rev 1, "NCR Quality Trending" (Attachment 1D-H, *WI 070002, Rev 1, NCR Quality Trending*), CCR review was mistakenly left out of the CAPA trends meeting for (b) (4) due to an incorrect interpretation of the newly revised procedures.

As an initial correction, CCR trending review was re-instated as part of (b) (4) CAPA trend meetings and was included in the (b) (4) review held on 26 Apr 2018 (Attachment 1D-I, (b) (4) (b) (4) *Quality Systems Trend*). CCR tends will continue to be reviewed during (b) (4) CAPA trend meetings going forward. In addition, during the investigation into this Observation, Zimmer Biomet identified a disconnect between SOP 070001 (Attachment 1D-G), which requires NCR trending and by product family, defect code, and value stream and does not require CCR trending, and WI 070002 ()Attachment 1D-H), which does not require trending by product family, but does reference CCRs within its scope. Zimmer Biomet will revise both of these documents to clarify and align trending and review requirements across the two documents.

Finally, the Warsaw North Campus currently uses a validated spreadsheet to trend NCRs and CCRs. Zimmer Biomet has identified an opportunity to make the trending process more efficient by automating NCR and CCR trending directly from (b) (4) Zimmer Biomet's electronic NCR system. After the (b) (4) system is updated to facilitate this automatic trending, Zimmer Biomet will obsolete the NCR Trending Spreadsheet currently in use at the Warsaw North Campus.

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 1D-1 | Included trending of CCRs in (b) (4) CAPA Trend Meetings, beginning with the (b) (4) (Attachment 1D-I) | 26 Apr 2018 |
| 1D-2 | Updated CA-04031 to include the Observation 1(D) findings regarding trending of CCRs in the CAPA scope (Attachment 1D-A) | 11 May 2018 |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 1D-3 | Revise NCR Trending Spreadsheet to provide for trending by (b) (4) | (b) (4) |
| 1D-4 | CAPA CA-04031 Root Cause / Action Plan Phase Complete | (b) (4) |
| 1D-5 | Revise SOP 070001 and WI 070001 to update trending / review requirements for Defect Codes and Cause Codes and train personnel to revisions | (b) (4) |
| 1D-6 | Update (b) (4) to allow for trending directly from (b) (4) including multiple defect trending | To be provided in a future response |
| 1D-7 | Obsolete the NCR Trending Spreadsheet following the (b) (4) updates | To be provided in a future response |
| 1D-8 | CAPA CA-04031 Action Implementation Plan Phase Complete | To be provided in a future response |
| 1D-9 | CAPA CA-04031 VOE Phase Complete | To be provided in a future response |

**FDA Observation 1(E)**

**B. Only one defect code is assigned to NCRs having multiple deficiencies documented in a single record. On 4/18/2018, your Engineer Manager for Central Engineering stated that only the defect code is trended per *WI070002: NCR Quality Trending* (Rev. 1). For example, the following NCRs contain information regarding nonconformances that were not trended:**

| NCR # | Description/Findings | Defect Code |
|---|---|---|
| NCR12197758 | "tape gum, missing porous and discoloration" | SU01-Surface Defect |
| NCR12185478 | "2 parts have scratches on them. All 8 parts have fuzz particles." | MA03-Foreign Material |
| NCR12220917 | "1. Found fuzz all inside porous, 2. Found pits and scratches on the critical Surfaces" | MA03-Foreign Material |
| NCR12177720 | "1) Tape gum between porous and 30 grit surfaces. 2) Parts have been assembled and there is no approved rework" | MA03-Foreign Material |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Observation 1(E) Investigation and Response:**

On 02 Nov 2017, prior to the recent inspection, Zimmer Biomet opened CAPA CA-04031 (Attachment 1D-A, CAPA CA-04031, *Summary*) to improve the non-conforming product process at the Warsaw North Campus. After the inspection, Zimmer Biomet revised the scope of CA-04031 to include the findings from Observations 1(D), 1(E), and 6. CA-04031 is currently in the Root Cause / Action Plan Phase and is due to be promoted to the Action Implementation Phase by (b) (4) .

All defects for a given NCR are described in the narrative "Finding" field of the NCR record in the (b) (4) system. Under the current practice at the Warsaw North Campus, however, records that relate to multiple defects are only assigned one Defect Code. This practice is contrary to WQLT003 Rev 3, "Procedure –(b) (4) NCR System Procedure," which provides instructions on how to document multiple defect codes in Section C, Step 1 (Attachment 1E-A, *WQLT003, Rev 3, Procedure –* (b) (4) *NCR System Procedure*). Despite these instructions, the current documentation practice makes it difficult to properly trend NCRs by defect types. As an initial containment / correction, instructor-led training was conducted on the coding requirements of WQLT003 Rev 4 "Procedure –(b) (4) NCR System Procedure" (Attachment 1E-B, *Training Evidence*), which was recently updated (Attachment 1E-C, *WQLT003, Rev 4, Procedure-*(b) (4) *NCR System Procedure*) in order to make reference to the newly created INST 13.1.1.3 Rev 1 "(b) (4) NCR and CCR Defect Codes Definitions " (Attachment 1E-D, *INST 13.1.1.3, Rev 1,* (b) (4) *NCR and CCR Defect Codes Definitions*).

As discussed further in the response to Observation 6(B), operators are not consistent in their usage of Defect Codes for Warsaw North Campus NCRs. To address this gap, Zimmer Biomet revised and better defined Defect Code definitions in applicable procedures, as explained further in the response to Observation 6(B). Using these newly defined Defect Codes, Zimmer Biomet will remediate and conduct retrospective trending of a sample of NCRs. The remediation will include documenting multiple defect codes (with the new definitions) in NCRs that refer to multiple defects in the NCR narrative fields. Please see the response to Observation 6(B) for further details on this planned action.

In addition, as addressed in the response to Observation 1(D), Zimmer Biomet will update the (b) (4) system to improve our ability to trend NCRs. This improved trending process will include multiple Defect Code trending. Please refer to the response to Observation 1(D) for further details. While the (b) (4) system is being updated, Zimmer Biomet will update the NCR Trending Spreadsheet that is currently in use to allow for trending multiple defects in the interim.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 1E-1 | Conducted refresher training on the NCR coding instructions in WQLT003 Rev 3 (Attachment 1E-B) | 11 May 2018 |
| 1E-2 | Updated CA-04031 to include the Observation 1(E) findings regarding use of single defect codes in the CAPA scope (Attachment 1D-A) | 11 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 1E-3 | Update NCR Trending Spreadsheet to allow for multiple defect trending | (b) (4) |
| 1E-4 | CAPA CA-04031 Root Cause / Action Plan Phase Complete | (b) (4) |
| 1E-5 | Update the (b) (4) system to allow for trending directly from (b) (4) including multiple defect trending. | To be provided in a future response |
| 1E-6 | CAPA CA -04031 Action Implementation Phase Complete | To be provided in a future response |
| 1E-7 | CAPA CA-04031 VOE Phase Complete | To be provided in a future response |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 2

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 2**

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

***This is a repeat observation from the FDA inspection dated 9/12/2016 to 11/22/2016.***

**Specifically,**

**During the previous FDA inspection, the validation of (b) (4) sterilization Cycle (b) (4) was found to not provide objective evidence that devices are sterilized with an (b) (4) (b) (4) as purported by the validation report. The cycle was used to sterilize (b) (4) and Sports Medicine devices.**

**Since then, your firm has validated a new (b) (4) sterilization cycle (Cycle (b) (4)) which utilizes a new (b) (4) and (b) (4) totes (b) (4) However, Cycle (b) (4) was not revalidated and the studies performed in lieu of revalidation did not provide objective evidence that devices currently in distribution meet an (b) (4). For example:**

A. **Products sterilized by Cycle (b) (4) underwent technical review by (b) (4) sterilization SMEs to (b) (4) " (b) (4) (b) (4) Sports Medicine products failed to meet acceptance criteria and were subjected to (b) (4) cycle study. The study demonstrated that three (3) of the (b) (4) products were more difficult to sterilize than the (b) (4) historically used for Cycle (b) (4) Juggerknot 2.9MM/ Needles (item #110005096), Juggerknot Mini (item #912076), and Juggerloc B2B (item #110007345/110007337).**

B. **The three (3) products were then subjected to a (b) (4) minute) study. The study protocol (#201606011, Rev. 02, approved 1/13/2017 states (b) (4) The actual location used was not documented; however, on 4/13/2018, your Principal Sterilization Associate said he and his team placed the devices in the (b) (4) of the (b) (4) This (b) (4) study and Cycle (b) (4) utilized (b) (4) which only feature (b) (4) around the (b) (4) and (b) (4) . Justification for choosing the (b) (4) of the (b) (4) instead of the (b) (4) was not documented.**

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**C. A BI placed in (b) (4) location of one of the Juggerknot Mini device subjected to the (b) (4) (b) (4) study (item (b) (4) ) failed sterility testing. Subsequently, your firm subjected the failed product to a (b) (4) minute) study, in which all BIs tested negative for growth. Again, the actual location in which the products were placed was not documented, but your Principal Sterilization Associate said he and his team used the (b) (4) of the (b) (4) Justification for this location was again not documented.**

**D. The (b) (4) and (b) (4) studies do not demonstrate repeatability of the Cycle (b) (4) sterilization process. *SOP 9.4.4:* (b) (4) *Process Validation Method* (Rev. 5, effective 9/14/2011) states "(b) (4) ." Your firm's (b) (4) sterilization SME confirmed this was not a validation."**

**Observation 2 Investigation and Response:**

At the outset, Zimmer Biomet would like to clear up a misunderstanding in the Observation. The Observation states that the studies cited in the Observation were performed "in lieu of revalidation" of the previous (b) (4) sterilization process, referred to as "Cycle (b) (4) This is inaccurate; the (b) (4) studies referenced in parts A, B, and C of the Observation were never intended to replace a revalidation of Cycle (b) (4). Cycle (b) (4) had been fully validated, as explained in the response to Observation 1(B) from the 2016 FDA-483, and no revalidation was needed; further, Cycle (b) (4) remained validated, as evidenced by the fact that it passed all of its annual re-qualifications. The studies referenced in this Observation were annual re-qualification studies intended to determine the continued appropriateness of the sterilization cycle to deliver sterile products for the current Warsaw North Campus product portfolio of (b) (4) and Sports Medicine products. Although Zimmer Biomet has since implemented a new, validated (b) (4) sterilization process, Cycle (b) (4), the company nevertheless remains confident that the previous cycle, Cycle (b) (4) was appropriate for use and that it resulted in the release of sterile product.

Original Cycle (b) (4) Validation (2003)

In March 2003, Zimmer Biomet validated (b) (4) Sterilization Cycle (b) (4) (Biomet Report #79, approved 14 Mar 2003), which fulfilled the requirements of the then-current standard, ANSI/AAMI/ISO 11135-1994. Consistent with the ISO 11135 standard, the original validation demonstrated the reproducibility of the sterilization process to provide product sterile to an (b) (4) or greater. The validation studies were comprised of (b) (4) study in the

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

(b) (4) chamber, (b) (4) cycles, and (b) (4) cycle. The original validation activity, in conjunction with successful (b) (4) re-qualification studies (b) (4) demonstrates the repeatability of this process to achieve a (b) (4) for the validated product. Further details about the initial validation of Cycle (b) (4) were provided to FDA in the initial response to Observation 1(B) of the 2016 FDA-483.

Finally, Zimmer Biomet notes that a load temperature distribution study was conducted as part of the original Cycle (b) (4) validation in 2003 validation. The study included (b) (4) thermocouples that were distributed across the (b) (4) pallet load. The data from this study demonstrated a uniform temperature across the product load, as evidenced by temperatures that were within (b) (4) F spread across the (b) (4) load positions. This minor temperature differential was well within the ISO 11135 standard at that time, which recommended this temperature spread to be within (b) (4) °F.

(b) (4) Studies (2016–2017)

Zimmer Biomet's update responses to Observation 1(B) of the 2016 FDA-483 described in detail the (b) (4) sterilization expert's review and the (b) (4) cycle studies that are cited in Observation 2 parts A through C. As stated above, the studies were not intended to revalidate Cycle (b) (4), nor to replace a full revalidation. Rather these studies were intended to demonstrate, through objective evidence, the continued appropriateness of the sterilization cycle to render sterile products for the current portfolio. Each of these studies is summarized below.

In September 2016, (b) (4) conducted a review of the Cycle (b) (4) product portfolio to assess potential for gaps in product adoption into the (b) (4) Sterilization Cycle (b) (4) This review assessed worst case product/packaging features for (b) (4) sterilization. The identified worst case challenge products were selected based upon the devices' associated design features and packaging configurations that included a (b) (4) which is placed in (b) (4). The principal challenge for these devices was the product within the (b) (4). The (b) (4) packaging configuration, as well as (b) (4) allows for sufficient open space within and between (b) (4), and therefore is no more challenging of a product arrangement than the validated configuration.

As a result of the experts' assessment, Zimmer Biomet performed a (b) (4) study in December 2016 to determine (b) (4) of the (b) (4) most challenging products/features as part of the annual re-qualification of the validated sterilization process. In

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

the (b) (4) study, (b) (4) products were found to have resistances greater than the (b) (4) (b) (4) Zimmer Biomet then performed the (b) (4) and (b) (4) (b) (4) studies (as referenced in the Observation) in January 2017 to confirm that these most challenging products could be sterilized through Cycle (b) (4). The results confirmed that an (b) (4) (b) (4) was achieved for all worst case product for Cycle (b) (4). All three studies—the (b) (4) (b) (4), and (b) (4) —served their purpose, which was to ensure that the already validated Cycle (b) (4) was appropriate for sterilization of the newly identified most challenging products and features.

As reported in the Observation, during the (b) (4) and (b) (4) studies, the test products and biological indicators (BIs) were placed in the (b) (4) of the (b) (4) Zimmer Biomet, (b) (4) selected this location based on: (1) the temperature study performed within the (b) (4) of the original 2003 (b) (4) (b) (4) validation which showed a temperature difference of no more than (b) °F across (b) (4) locations within (b) (4) across a (b) (4) pallet load; and (2) the assessment by a sterilization expert in accordance with AAMI TIR:16. (b) (4), stated that the (b) (4) of the (b) (4) would be the (b) (4) location in the product configuration to achieve optimum sterilization conditions for lethality to effectively occur and therefore is an appropriate location for the BIs. Zimmer Biomet acknowledges, however, that this justification was not documented in the study protocol or study reports. Zimmer Biomet has since drafted a final summary report ((b) (4)) to document this justification and results of these studies. (Attachment 2-C, *Project 662*).

In the 2016 and 2017 studies, BIs placed in the most challenging location ((b) (4) (b) (4)) demonstrated kill in both a (b) (4) and (b) (4) that met the requirements specified in the AAMI sterilization standard.

Finally, it is important to note that a (b) (4)) with zero positive BI results demonstrates a high factor of safety, (b) (4) (as estimated by using the (b) (4)). This equates to an (b) (4) (b) (4) (b) (4) (b) (4) cycle.

Thus, in summary, the (b) (4), and (b) (4) studies conducted in 2016 and 2017 for Cycle (b) (4) demonstrate (1) that the worst case product that is more resistant than the (b) (4) achieves a (b) (4) and (2) a minimum of an (b) (4) (b) (4) for the worst case product. In addition, Zimmer Biomet reiterates that the (b) (4) and (b) (4) studies were not considered a validation, nor were they intended to substitute for a re-validation, but rather the cycles were the annual requalification of validated Cycle (b) (4)

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Chemical Indicator Study (2018)

During the recent inspection and in response to a concern raised by one of the FDA investigators regarding (b) (4) in the (b) (4), Zimmer Biomet developed and performed a chemical indicator study to confirm sufficient (b) (4) into the (b) (4), which have gaps only at the (b) (4). (Attachment 2-D, *Project 661*). Zimmer Biomet conducted this study solely to demonstrate to the investigator the (b) (4) in all areas of the (b) (4) and the results were provided verbally during the closing meeting on 24 Apr 2018. In this study, (b) (4) were placed at the (b) (4). The (b) (4) used were consistent with the (b) (4) used from 2003 to 2017 for Sports Medicine and (b) (4) products in Cycle (b) (4). All chemical indicators responded to the presence of (b) (4) with a color change (b) (4), thereby demonstrating the presence of (b) (4) all locations (b) (4) during Cycle (b) (4)

We note that Zimmer Biomet had not previously conducted a study like this one because this type of (b) (4) testing is not required by the AAMI/ISO 11135 standard, nor is it industry standard or best practice.

Taken together, the original Cycle (b) (4) validation, the 2016-2017 requalification comparative resistance and (b) (4) studies, and the chemical indicator study demonstrating the presence of (b) (4) throughout the (b) (4) provide substantial objective evidence that an (b) (4) was consistently delivered for the entire product scope for the historical use of Cycle (b) (4) Until the adoption of Cycle (b) (4), there were no significant changes to Cycle (b) (4) or (b) (4) since the original 2003 validation. Zimmer Biomet is therefore confident that product sterilized and released to the market under Cycle (b) (4) was in fact successfully sterilized.

As part of Zimmer Biomet's commitment to continuous improvement, Zimmer Biomet is no longer using Cycle (b) (4), as previously reported in the update responses to the 2016 FDA-483. In addition, Zimmer Biomet redesigned the (b) (4) to increase (b) (4) efficiency. All (b) (4) products have been transferred to (b) (4) as of November 2017 and all (b) (4) Sports Medicine products have been transferred to (b) (4) as of December 2017. The Cycle (b) (4) validation was reviewed by one of the FDA Investigators during the recent inspection, with no issues cited.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 2-1 | Completed final summary report for 2016-17 (b) (4), (b) (4) and (b) (4) Study (Attachment 4-C) | 18 Apr 2018 |
| 2-2 | Conducted chemical indicator study to confirm (b) (4) (b) (4) n throughout the (b) (4) used in Cycle (b) (4) (Attachment 4-D) | 09 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| N/A | Zimmer Biomet considers this Observation closed and does not anticipate any further actions | N/A |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 3

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 3**

**Risk analysis is inadequate.**

**Specifically,**

**Per your Design Control Procedure, QM 4.3, Rev 10, risk management activities shall occur pursuant to Risk Management Procedures QM 4.4, and shall be incorporated in the design history file as defined in SOP 4.4.1 Design Risk Management and SOP 4.4.2 Process Risk Management.**
**You establish a risk priority number (RPN) for your PFMECA's as a mathematical product of the (b) (4), with RPN scores of (b) (4) or more requiring further mitigation.**
**A review of PFMECA PF0700, Rev 4, regarding Sterile Packaging found the following:**

A. **Inconsistences in the assignment of severity scores for failure modes with the same "Potential Failure" effects. For example, the failure effect of "Compromise of the product Sterility" is given severity of scores of (b) (4) (necessitates minor medical intervention) or (b) (4) (results in permanent impairment of body function or damage to body structure/ necessitates surgical intervention) for different potential failure modes. This failure effect regarding sterility was assigned a level of (b) (4) for (b) (4) line items and a level of (b) (4) if (b) (4) line items in this PFMECA. Using a severity level of (b) (4) for the failure effect of product sterility for al failure modes would result in (b) (4) of the hazard lines exceeding the acceptable level of (b) (4) and requiring further mitigation.**

B. **Your assignment scores of the potential severity rating in your PFMEA for the possible outcomes related to sterility issues, such as infection, are not commensurate with your current Master Harms Index, CF03000, Rev 2., which links harm descriptions to the severity of the harm. For example, the harm of infection has a potential severity as high as (b) (4) ((b) (4) "Catastrophic") in your Master Harms Index for a severe systemic infection including sepsis. Your PFMEA assigns scores of (b) (4) or (b) (4) as potential severity levels associated with the failure effect of compromising of product sterility.**

**Observation 3 Investigation and Response:**

On 07 Feb 2018, prior to the recent inspection, Zimmer Biomet opened CAPA CA-04257 (Attachment 1C-B, CAPA CA-04257, *Summary)* to update risk management files at the Warsaw North Campus for compliance with ISO 14971:2012. CA-04257 is currently in the Root Cause /

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Action Plan phase and is due to be promoted to the Action Implementation Phase on (b) (4) (b) (4) CA-04257 is linked to CA-02719 (Attachment 1C-A, CAPA CA-02719, *Summary*), which was opened on 19 Jul 2016 to manage the design history file (DHF) remediation occurring under (b) (4) . After the inspection, Zimmer Biomet revised the scope of CA-02719 to include the findings from Observation 3 regarding assessment of risk severity in process failure modes and effects analyses (pFMEAs). CA-02719 is currently in the Action Implementation Phase and is due to be promoted to the Verification of Effectiveness Phase by (b) (4) .

Zimmer Biomet reviewed the findings of this Observation jointly with the findings in Observation 1(C) related to assignment of risk values in legacy design files. To minimize the opportunities for future inconsistencies in risk assessments, Zimmer Biomet has decided to assign risk severity scores only in the product dFMEAs, and will no longer assign separate risk severity scores in the pFMEAs. The remediation of dFMEAs is discussed in detail in the response to Observation 1(C).

This change will be implemented through revisions to the corporate risk management procedure CP03000, "Risk Management System." (Attachment 3-A, *Change Request Log Numbers QSP00501, SOP002004, and SOP002003*). In addition, the pending revisions to CP03000 will also outline all risk management requirements of ISO 14971 and FDA Guidance for Industry "Quality Risk Management" for Product Characterization, dFMEA, uFMEA, and pFMEA. Risk control measures for design inputs will be identified in the dFMEAs and uFMEAs. If the design inputs and associated specifications are connected to a risk control measure mitigating a risk, then the specifications connected to these design inputs are controlled in the manufacturing process through process validations and inspections. FALs (First Article Inspections) are performed on all dimensions irrespective of the relation to risk control measures at the initial release of the product and at any subsequent changes to the part. However, under the revisions to CP03000, the process criticality will be assigned based on the severity associated with the relevant design input and associated specifications in the dFMEA and uFMEA; the criticality will not be independently assigned in the pFMEA. Rather, the pFMEA will only identify the probability of failure and the probability of detection of the failure.

Zimmer Biomet will remediate and revise existing pFMEAs under (b) (4) and CA-02719 during the DHF remediation process. Zimmer Biomet will also revise and correct the risk ratings in the dFMEAs and uFMEAs. All revisions will be made consistent with the requirements of revised CP03000.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

When documenting the process risk index and associated pFMEA for each manufacturing process during (b) (4) DHF remediation, if Zimmer Biomet identifies a manufacturing process that is not associated with an existing pFMEA, Zimmer Biomet will open an IE to address the gap. (Attachment 3-B, *CA-02719, Rev 1, Process Risk Index for Design History Files within* (b) (4) ).

Despite the historical inconsistencies in the assignment of severity scores for failure modes in the Warsaw North Campus pFMEAs, Zimmer Biomet's listening and trending systems are intended to ensure that unanticipated risks and occurrences are identified and that patients are/were not subjected to unreasonable risks due to any potential inconsistencies or errors in pFMEA severity scores and the absence of proper mitigations that could result, as described below.

First, nonconforming product reports (NCRs) opened during the manufacturing process address internal failures due to manufacturing process. Under SOP 13.1.1, (b) (4) NCR Trending," NCRs are trended (b) (4) and, if any issues are identified, then Zimmer Biomet escalates the NCRs through its standard processes by opening an Issue Evaluation (IE), CAPA, and/or SCAR as appropriate. If any products subject to the escalated NCRs are suspected to have been released to the field, then Zimmer Biomet initiates its HHED for evaluation of potential field actions.

Second, per CP04007, "Complaint Trending," Zimmer Biomet performs (b) (4) complaint trend analyses to identify alleged deficiencies in released product, including manufacturing failures. Identified triggers are processed through management review and the Issue Evaluation process. In addition to (b) (4) complaint trending, WI040006, "Complaint Investigation," requires that an occurrence calculation be completed in instances where a definitive root cause of the reported failure is identified and compared to the expected occurrence rate as outlined in the FMEA. If the occurrence rate exceeds the expected occurrence rate or if the failure mode is not listed in the risk document, the functional area manager is contacted and an Issue Evaluation is opened.

Third, complaints that allege product failed or are non-conforming before first use are considered Complaints Out of Box (COOBs). COOBs are independently monitored as part of the complaint handling process, and are included within complaint trending, (b) (4) CAPA trending, and Management review meetings. Zimmer Biomet procedure CP04006, "Complaint Investigation," currently requires escalation for further analysis of all confirmed COOBs that resulted in patient impact, which includes review of the pFMEA, as applicable.

Fourth, Zimmer Biomet conducts (b) (4) CAPA trending under SOP070001, "Quality system Trend Review." Under this procedure, the following quality data is reviewed during (b) (4)

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

CAPA trending meetings: nonconformance rate, combined field actions per (b) (4), process monitoring, process validation failures, product holds, HHEs, sterilization and environmental data, lot defective rate, and combined supplier. If any action limits are exceeded, Zimmer Biomet opens a new IE or confirms that an existing IE, CAPA or NCR will be used to investigate and correct the issue.

Fifth, during (b) (4) Quality Management review meetings, the Quality Management team reviews NCR trending, complaint trending, process monitoring, product holds, process validation failures, and lot defective rate, as per SOP016000, "Quality Management Review." Again, if any trends are identified, then according to several Zimmer Biomet procedures (including CP01602, "Global Quality Management System key performance indicators," QM 14.0, "Corrective and Preventive Action," CP04007, "Complaint Trending," SOP070001, "Quality System Trend Review, and SOP 9.3.4, "Process Monitoring of Validated Process"), if any action limits have exceeded a new IE is opened or an existing IE, CAPA or NCR will be used to investigate and correct the issue per SOP01600 , "Quality Management Review."

Finally, as reported in more detail in the response to Observation 1(C), Zimmer Biomet previously completed Device Performance Reviews (DPRs) for each Warsaw North Campus product line as part of (b) (4). The DPRs support continued distribution of product while design history file (DHF) remediation is ongoing.

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 3-1 | Revised scope of CA-02719 to include in its scope the findings in Observation 3 regarding inconsistent severity ratings in legacy pFMEAs (Attachment 1C-A) | 09 May 2018 |
| 3-2 | Initiated revisions to CP03000 to streamline the Risk management process by which the manufacturing process controls are determined by dFMEA and uFMEA severity ratings (Attachment 3-A) | 10 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 3-3 | CAPA CA-04257 Root Cause / Action Plan Phase Complete | (b) (4) |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| | | |
|---|---|---|
| 3-4 | Implement revisions to CP03000 to streamline the Risk management process by which the manufacturing process controls are determined by dFMEA and uFMEA severity ratings | (b) (4) |
| 3-5 | Train personnel to revised CP03000 Procedures | (b) (4) |
| 3-6 | Remediate existing pFMEAs under (b) (4) DHF review to remove risk severity ratings | (b) (4) |
| 3-7 | CAPA CA-04257 Action Implementation Phase Complete | To be provided in a future response |
| 3-8 | CAPA CA-04257 VOE Phase Complete | To be provided in a future response |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 4

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 4**

**Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been adequately established.**

***This is a repeat observation from the FDA inspection dated 9/12/2016 to 11/22/2016.***

**Specifically,**

**Your firm did not ensure adequate test methods are used by your contract lab, Supplier A. Per SOP 28.0.1, "Process Monitoring of Final Cleaning," Revision 9, testing for all products without an approved cleaning validation is required to undergo (b) (4), (b) (4) and (b) (4) testing. This testing is contracted to supplier A or your firm for adequacy of use with your firm's products.**

**For example, there are (b) (4) unique types of polymer materials used at your firm's location:**

(b) (4)

**None of these (b) (4) polymers have a documented justification on why the current test methods are acceptable for the unique materials. Additionally, there is no documented justification that all of your firm's products do not present a new worst case scenario for the current test method.**

**Observation 4 Investigation and Response:**

On 04 May 2018, Zimmer Biomet opened CAPA CA-04509 (Attachment 4-A, CAPA CA-04509 *Summary*) to investigate and address the findings regarding test methods for process monitoring of Warsaw North Campus cleaning processes in Observations 1(B) and 4. CA-04509 is currently in the Root Cause/Action Plan Phase and is due to be promoted to the Action Implementation Phase by (b) (4)

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Cleaning Process Monitoring Testing for Polymer-Based Products

Zimmer Biomet's testing lab uses validated test methods to conduct the process monitoring tests for polymer-based product produced at the Warsaw North Campus. Although the test method was validated using (b) (4) ), Zimmer Biomet nevertheless has conducted testing and analyses sufficient to adopt the polymer materials listed in the observation into this validated test method.

Zimmer Biomet's test lab validated these test methods in June 2009 for (b) (4) (Attachment 4-B , *Method Validation for Quantitative Analysis of* (b) (4) *{MV-7033 r1.0}*; Attachment 4-C, *Method Validation for* (b) (4) *Orthopaedic Implantable Devices {MV-7038 r1.0}*). UHMWPE is tested for (b) (4) as per the requirements of ZWI 29.532 (Attachment 4-D, *ZWI 29.532, Rev 3,* (b) (4) *Orthopaedic Implantable Devices*) and for (b) (4) using ZWI 29.510 (Attachment 4- E, *ZWI 29.510, Rev 4, Quantitative Analysis of* (b) (4) *Orthopaedic Implantable Devices*). Both of these methods are gravimetric tests (using beaker weights) and have been validated for use under MV-7038 (b) (4) and MV-7033 (b) (4) ). In these test method validations, Zimmer Biomet established multiple analytical performance characteristic requirements, including (b) (4) The (b) (4) ) far exceeded the requirement of greater than (b) (4) as specified in ASTM F2459, section 10.3 for both methods.

(b) (4)

For the (b) (4) product used for the test method validation in (b) (4) and (b) (4), there are no production contact materials besides cleaning and biological upgrade. Therefore, the inoculants used for these test method validations were chosen because they represented potential environmental contaminants. (b) (4) is a common machine lubricant which is soluble in (b) (4) . The inoculant for the (b) (4) was (b) (4) which is soluble in water.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Polymer Adoptions

As stated above, the validated test methods assess beaker weight, not product weight. If (b) (4) (b) (4) r or (b) (4) attack or dissolve the base material, any dissolved polymer will be contained in the beaker and measured as a contaminant. It can only add to the measured contaminant, it cannot subtract/mask other contaminants. Therefore, the test method provides a conservative measure of contact materials contaminants. Zimmer Biomet's current practice for adoption of new polymeric materials into the test method concluded that if the test method on a new polymeric base material yields results that pass the acceptance criteria, then the base material is not being attacked/dissolved by the solvents. On the other hand, if the base material is not compatible with the solvent, (b) (4) Zimmer Biomet has used his adoption process for several polymers, as described below.

Zimmer Biomet adopted (b) (4) into the existing TMVs in March 2017, as documented in ZTR_WA_0423_16 (Attachment 4-F, (b) (4) All results for (b) (4) ), and (b) (4) were below the limit of quantification (LOQ). Zimmer Biomet concluded that, because these tests are performed either as beaker weight ((b) (4) ) or (b) (4) (b) (4) ), the solvents used in the test methods did not attack or dissolve the base material and, therefore, (b) (4) could be adopted into the existing TMVs.

In February 2017, Zimmer Biomet adopted additional polymers into the existing TMVs. Specifically, (b) (4) were adopted into the TMVs as described in ZTR_BI004_17 and ZTR_BI_0005_17 (Attachment 4-G, (b) (4) *, Biomet Sports Medicine Cleanliness Study Part* (b) (4) and (Attachment 4-H, (b) (4) *, Biomet Sports Medicine Cleanliness Study Part* (b) (4) ). In (b) (4) , all results for (b) (4) were below LOQ of the test methods. The results for (b) (4) and (b) (4) met acceptance criteria with process capabilities of a Ppk (b) (4) ((b) (4) respectively). The Ppk values are used here to show that sufficient numbers of material/samples were run to support the conclusion that raw material variation was not an issue with solvent compatibility; the Ppks are not being used to show method capability. The results from (b) (4) were below LOQ for all tests (i.e., (b) (4) (b) (4) ). As explained above, because these tests utilized (b) (4) (b) (4) or (b) (4) , the results provide objective evidence that the polymer base materials are not being attacked or dissolved by the solvents and that the polymer base materials can be adopted into the existing TMVs.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

In addition, Zimmer Biomet has further evaluated the polymers used in production of implantable devices at the Warsaw North Campus. This evaluation, described below, provides further rationales for adopting additional polymers into the test methods validated using UHMWPE.

First, for all of the materials in (b) (4) Sports Medicine products (i.e., (b) (4) (b) (4)), Zimmer Biomet (b) (4) and are not subjected to additional contact materials prior to packaging. Therefore, there are no known contact materials to test for. As an example, exhaustive extraction per USP <661> USP Physicochemical Tests for Plastics was performed by (b) (4), on the (b) (4) implant which includes (b) (4) and found non-volatile residue of (b) (4) mg. (Attachment 4-I, *Report* (b) (4)). Further, based on the original test method validations as described above, there is negligible risk that the test methods would fail to detect environmental contaminants that would not be soluble in either (b) (4) and/or (b) (4). As such, no containment is required for these products.

Second, (b) (4) is utilized in (b) (4) that are (b) (4) (b) (4). These (b) (4) components are (b) (4) in a clean room (b) (4). There are no intentional contact materials. (b) (4) has chemistry similar to (b) (4). Given that there are no intentional contact materials and the (b) (4) has a similar chemistry to (b) (4), there is negligible risk that the validated test methods would fail to detect environmental contaminants on (b) (4) and, accordingly, no containment is required for (b) (4).

Third, (b) (4) can be (b) (4). The only intentional contact material is a (b) (4) utilized for the (b) (4) (b) (4) material. All machining is performed (b) (4). The (b) (4) (b) (4) if transferred to the (b) (4) (b) (4) material, would be on the order of mere nanometers in thickness and would not be quantifiable via gravimetric techniques. Therefore, the process monitoring for (b) (4) is performed via (b) (4) testing. Given that there are no other intentional contact materials and there is negligible risk that the test methods would fail to detect environmental contaminants, as described above, no containment is required for (b) (4) products.

To date, we have not identified (b) (4) as an implantable material, but we continue to review for all implantable (b) (4) materials used at the Warsaw North Campus to verify that the current, validated test methods for (b) (4) are applicable to these materials. (b) (4) has been identified as packaging ((b) (4)) or as an instrument component that has only transient patient contact.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

To ensure that test method validation adoptions are consistently performed and documented, Zimmer Biomet will revise section 8.8.2.3 of SOP 095260, "*Test Method Validation*" (Attachment 4-J, *SOP 095260, Rev 1, Test Method Validation*) to require consideration and documentation of a rationale why adoption of new base materials or worst-case manufacturing methods (e.g., residual particulates from a (b) (4) process) conditions would not have any impact on the performance criteria of the existing, validated cleaning test methods.

Process Monitoring Testing for (b) (4) Product

As referenced in Observation 1(B), Zimmer Biomet will evaluate the existing test method validations for particulates and (b) (4) ) particularly as they relate to testing of product that has undergone a (b) (4) process. This is also proceeding under CA-04509.

As explained above, due to the beaker weight test method (b) (4) failures due to the presence of particulates will generate false positives but are not likely to generate false negatives. Therefore, even in the event that the current (b) (4) process, or other (b) (4) processes, result in the presence of (b) (4) particulates on the product, Zimmer Biomet is unlikely to accept parts that are in fact out of specification. (See further justification below.) In addition, under current procedure, issue evaluation files (IEs) are opened for all (b) (4) out-of-specification results.

As part of the investigations for OOS results from (b) (4) extraction since January 2018, if the (b) (4) results are at or above LOQ, secondary testing is performed to identify the potential residue and, if requested by a quality or manufacturing engineer, to quantify the (b) (4) in the sample. A flowchart of this investigation practice is included as (Attachment 4-K, *Workflow for* (b) (4) *Extraction Including Investigation Workflow)*. Specifically, Zimmer Biomet uses a FTIR test to quantify (b) (4) in residual material in the beaker after a positive test result. The test method validation, WVTMV-000150, was approved on 03 Nov 2017 and was formalized in ZWI 29.508 Rev 3, "(b) (4) which became effective 08 Jan 2018. (Attachment 4-L, *WVTMV-000150, Method Validation, FTIR analysis of* (b) (4) *residuals*).

Since the residual (b) (4) was implemented, all (b) (4) failures under SOP 28.0.23, (Attachment 4-M, SOP 28.0.23, Rev 2, (b) (4) *)* have been subjected to Fourier-transform infrared spectroscopy (FTIR) analysis to identify the chemical nature of the residual. Further, (b) (4) of those (b) (4) failures have also undergone (b) (4) quantification. In (b) (4) of the (b) (4) quantifications, the amount of (b) (4) identified was less than the

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

limit of detection (LOD); Zimmer Biomet only identified (b) (4) residue in (b) (4) of the (b) (4) FTIR identifications. The (b) (4) quantification for that test was (b) (4), but below (b) (4). This testing provides support for the earlier statement that the (b) (4) test method is not likely to have generated false negatives.

Going forward, all out-of-specification results for SOP 28.0.23 (Attachment 4-M), will undergo (b) (4) FTIR quantification to determine whether (b) (4) is the cause of the (b) (4) failure and whether the cleaning process is still adequate to remove manufacturing residuals. Zimmer Biomet intends to modify SOP 28.0.1, (Attachment 4-N, SOP 28.0.1, Rev 9, *Process Monitoring of Final Cleaning*) to address monitoring solvent extraction samples.

With respect to (b) (4) product already monitored through the existing cleaning TMV and released, Zimmer Biomet is confident that the product already released to the market did in fact pass its cleaning process monitoring. First, the inherent capability of the test method for quantifying (b) (4) is evidenced by the fact that the monitoring has in fact identified out of specification results in the past. Second, an additional test method was validated (WVTMV-000150, "FTIR analysis of (b) (4)") to quantitatively measure the amount of (b) (4) analysis of the eluant to determine if the (b) (4) failure was due to the presence of (b) (4). The (b) (4) is designed to detect (b) (4) as these (b) (4) are soluble in the (b) (4). The eluant sample measures only what is dissolved in the solvent and therefore does not measure the insoluble particulate. This method does not have acceptance criteria because it is used to provide additional information which can be used as part of the dispositioning of non-conforming product via NCR process or for appropriate containment and/or correction per procedures.

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 4-1 | Opened CAPA CA-04509 to investigate and address the findings regarding test methods for process monitoring of Warsaw North Campus cleaning processes (Attachment 4-A) | 04 May 2018 |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| | | |
|---|---|---|
| 4-2 | Initiated change request for revision to SOP 095260 to require consideration and documentation of a rationale why adoption of new base materials or worst-case manufacturing conditions would not have any impact on the performance of validated cleaning test methods (Attachment 4-O, *Change Request MC0000193306*) | 10 May 2018 |
| 4-3 | Initiated change request to revise SOP 28.0.1 to require (b) (4) FTIR quantification for (b) (4) failures (Attachment 4-P, *Change Request MC0000189047*) | 10 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 4-4 | CAPA CA-04509 Root Cause / Action Plan Phase Complete | (b) (4) |
| 4-5 | Develop and execute protocols to adopt new polymeric materials into test method validations | To be provided in a future response |
| 4-6 | Revise SOP 095260 to require consideration and documentation of a rationale why adoption of new base materials or worst-case manufacturing conditions would not have any impact on the performance of validated cleaning test methods | To be provided in a future response |
| 4-7 | Train personnel to the revisions to SOP 095260 | To be provided in a future response |
| 4-8 | Revise SOP 28.0.1 to require (b) (4) FTIR quantification for (b) (4) failures | To be provided in a future response |
| 4-9 | Train personnel to the revisions to SOP 28.0.1 | To be provided in a future response |
| 4-10 | CAPA CA-04509 Action implementation Phase Complete | To be provided in a future response |
| 4-11 | CAPA CA-04509 VOE Phase Complete | To be provided in a future response |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 5

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 5**

**Procedures to control environmental conditions have not been adequately established.**

***This is a repeat observation from the FDA inspection dated 9/12/2016 to 11/22/2016.***

**Specifically,**

**FDA Observation 5(A)**

A. **Environmental excursions have not been adequately investigated. All versions of IC 001: Increased Environmental Monitoring of Work Environments, and cleanrooms and *SOP 9.5.15 : Environmental Monitoring of Environmentally Controlled Areas* effective since 3/17/2017 require confirmed environmental action-limit excursions to be investigated via an NCR. Since 3/24/2017, at least (b) (4) NCRs have been initiated for microbial environmentally action-limit excursions. At least 23 of these (b) (4) excursions have not been adequately investigated. Specifically, the investigations documented in the ~~24~~ 23 NCRs were limited to re-sanitization and retesting. Investigations into the cause of the excursions were not documented.**

**Observation 5(A) Investigation and Response:**

On 08 May 2018, Zimmer Biomet initiated CAPA CA-04523 (Attachment 5A-A CAPA CA-04523, *Summary*) to address the issue identified in Observation 5 concerning lack of adequately investigated environmental action limit excursions. CAPA CA-04523 is currently in the Correction phase. CAPA CA-04523 is scheduled for promotion to Root Cause Analysis phase by (b) (4) .

The version of SOP 9.5.15, Environmental Monitoring of Environmentally Controlled Areas (Attachment 5A-B, *SOP 9.5.15, Rev 3, Environmental Monitoring of Environmentally Controlled Areas*) in place at the time of the inspection contained detailed guidance on actions to be performed in response to an environmental action limit excursion, regardless of the investigation of the excursion. These requirements are summarized below:

- Section 7.2.3.2: When monitoring results exceed action level/limits established in the applicable INST or an adverse trend is observed, the occurrence shall be investigated immediately. The results of investigation activities are to be documented on a combination of R-02437 (Environmental Out-Of-Limit Report) and in the NCR.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

- Section 7.2.3.3: The product area is shut down until correction can be made and confirmed via resampling of the location. Successful resampling results are reviewed by a Quality Assurance representative prior to the area being returned to service.
- Section 7.2.3.7: Notifications are sent to affected individuals / departments including: Environmental Services, Production, Plant Engineering, and Quality Assurance.
- Section 7.2.3.8: (b) (4) excursions of the action limits of the same test in the same room within a (b) (4) period shall result in an escalation to the CAPA process.

These actions were taken for each of the 23 NCRs identified in Observation 5(A) as having inadequate investigations.

Although the actions defined in the procedure were clear, the procedure lacked clear guidance on the requirements of the investigation of the action limit excursion. As an immediate correction in response to Observation 5(A), Warsaw North created the NCR procedure INST 13.1.1.4 (Attachment 5A-C, *INST 13.1.1.4, Rev 1, Environmental Excursion Investigations*) to correct this deficiency. The newly created procedure includes detailed instructions for investigating NCRs for environmental excursions. These instructions require:

- A clear problem statement
- An analysis of relevant data from historical performance of the area and surrounding / input areas to help focus the investigation
- An initial root-cause analysis
- Confirmatory testing and verification to ensure root cause is correct
- Final root-cause analysis
- Correction and/ or Corrective Action to prevent reoccurrence

Zimmer Biomet initiated a related site-wide training program to reiterate the existing requirements for environmental excursions and to train all involved individuals on the investigational requirements to the newly created INST 13.1.1.4. (Attachment 5A-C).

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 5-1 | Initiated CAPA CA 04523 to address the findings in Observation 5(A) regarding NCR investigations for environmental action limit excursions (Attachment 5A-A) | 08 May 2018 |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| | | |
|---|---|---|
| 5-2 | Created INST 13.1.1.4 to provide detailed instructions for the investigation of NCRs opened for environmental action limit excursions | 11 May 2018 |
| 5-3 | Implemented site-wide training to reiterate the existing requirements and train personnel on the revised investigational requirements in INST 13.1.1.4 | 11 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 5-4 | CAPA CA-04523 Correction / Containment Phase Complete | (b) (4) |
| 5-5 | CAPA CA-04523 Root Cause / Action Plan Phase Complete | To be provided in future response |
| 5-6 | CAPA CA-04523 Action Implementation Phase Complete | To be provided in future response |
| 5-7 | CAPA CA-04523 VOE Phase Complete | To be provided in future response |

**FDA Observation 5(B)**

**B. We observed employee practices that violate *SOP 9.5.17: Environmentally Controlled Areas: Cleanroom and Work Environment Practices* (Rev. 4, effective 2/1/2018), which instructs (b) (4) ." For example:**

**i. Employees load devices onto racks in an uncontrolled environment and place them onto (b) (4) which transport the loaded racks to environmentally controlled hoods. On 4/9/2018, we observed the racks present in (b) (4) (b) (4) Attached above the racks were "mailboxes" used to hold work order documentation. Interviews with employees revealed that racks are sent back to the uncontrolled environment via a pass-through. The racks are then reused without sanitizing the mailboxes.**

**ii. In the (b) (4) Work Environment on 4/9/2018, we observed an employee remove a sheet of "flower paper" from its open package on hi work station and take it into an environmentally controlled hood.**

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Observation 5(B) Investigation and Response:**

On 08 May 2018, Zimmer Biomet initiated CAPA CA-04521 to address the issues identified in Observation 5 (B) regarding employee practices that violated environmental controls procedures and practices(Attachment, 5B-A, CAPA CA-04521, *Summary*). CA-04521 is currently in the Correction phase and is scheduled to be promoted to the Root Cause Analysis phase by (b) (4) .

As reported in Observation 5(B), two specific instances were observed during the inspection wherein employees introduced into clean/controlled environment areas materials (i.e., mailboxes and flower paper) that were either un-sanitized or should not have been allowed to enter the area. Upon recognizing these errors, Zimmer Biomet removed the mailboxes and the flower paper from the clean / controlled environments where they were discovered, (Attachment 5B-B, *Change Request #191171*). After removing the mailboxes, a full sanitization of each affected area was performed.

Further, several additional corrections were made to ensure immediate containment of the issue. These included:

- An informal training was conducted with all the affected operators at each (b) (4) to ensure that requirements for clean / environmental control area entry of all items was completely understood.

- An ad-hoc assessment of all other clean / controlled environment areas of the facility was immediately performed to ensure that un-sanitized items of any kind (equipment, ancillaries, paper, etc.) were not inappropriately entering a controlled environment (Attachment 5B-C, *Aseptic Hood and Controlled Environment Area Audit*). All other un-sanitized items were either removed or are now being subject to a sanitization process before entering the area.

Zimmer Biomet assessed the current environmental controls procedure for adequacy related to transfer of items into clean / environmentally controlled areas. This review revealed a lack of clarity in the current procedure. On 19 Apr 2018, change request #191830 (Attachment 5B-D, *Change Request MC 191830*) was initiated to revise SOP 9.5.17, "*Environmentally Controlled Areas: Cleanroom and Work Environment Practices*". This revision will clarify the requirements for sanitization of materials and equipment in environmentally controlled areas. This change request will be released and implemented by (b) (4) .

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Further, Zimmer Biomet will perform a (b) (4) of all environmentally controlled areas to ensure the Warsaw North Campus facility is fully compliant with all environment control procedures. If any nonconforming conditions are identified, Zimmer Biomet will take appropriate actions, including containment and escalation to the CAPA process as needed and based on the risk associated with the audit finding.

Finally, Zimmer Biomet initiated (b) (4) Training (b) (4) to all individuals that work within, control material transfer into or out of, or enter a cleanroom/environmentally controlled area. This new training includes a series of (b) (4) Trainings in an effort to enhance the written procedures and includes the following:

- Introduction to Microbiology
- Introduction to Cleanrooms and Cleanroom Areas
- Environmentally Controlled Area/Cleanroom Gowning

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 5-1 | Conducted an ad-hoc assessment of all other clean/controlled environment areas at the Warsaw North Campus to ensure that un-sanitized items of any kind (equipment, ancillaries, paper, etc.) were not inappropriately entering a controlled environment | 09 Apr 2018 |
| 5-2 | Conducted informal training for affected operators (b) (4) (b) (4) to reinforce requirements for clean/environmental control area entry | 10 Apr 2018 |
| 5-3 | Removed the mailboxes and the flower paper from the clean / controlled environments where they were discovered | 13 APR 2018 |
| 5-4 | Initiated change request #191830 to revise SOP 9.5.17 to clarify the requirements for sanitization of materials and equipment in environmentally controlled areas | 19 Apr 2018 |
| 5-5 | Initiated (b) (4) Training (b) (4) | 03 May 2018 |
| 5-6 | Initiated CA-04521 to address the issues identified in Observation 5(B) regarding employee practices that violated environmental controls | 08 May 2018 |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 5-7 | CAPA CA-04521 Correction / Containment Phase Complete | (b) (4) |
| 5-8 | Perform a (b) (4) of all environmentally controlled areas to ensure the Warsaw North Campus facility is fully compliant with all environment control procedures | (b) (4) |
| 5-9 | CAPA CA-04521 Root Cause / Action Plan Phase Complete | To be provided in future response |
| 5-10 | CAPA CA-04521 Action Implementation Phase Complete | To be provided in future response |
| 5-11 | CAPA CA-04521 VOE Phase Complete | To be provided in future response |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 6

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 6**

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

***This is a repeat observation from the FDA inspection dated 9/12/2016 to 11/22/2016.***

**Specifically,**

**Your firm's procedures QM 13.1, "Control of Nonconforming Product," revs 4-8 and SOP 13.1.1, "Nonconforming Product Procedure," revs 3-7, do not ensure that nonconforming products are documented in a consistent manner. For example,**

**FDA Observation 6(A)**

**A. Your procedures do not ensure that your operators and engineers consistently open a NCR or CCR as required. For example,**

**i. SOP 13.1.1 does not clearly define when NCR or "common cause rework" (CCR) records should be initiated for nonconforming product. The procedure defines CCR as (b) (4) ." Per the procedure, NCRs are required to be formally investigated whereas CCRs are not.**

**On 4/16/2018, your Senior Quality Engineer II stated that the "common causes of NCRs" listed in Section 7.9 of the procedure in fact are cases where CCRs should be initiated. We observed inconsistency in whether NCRs or CCRs are initiated for apparently the same reasons. For example, CCR12224142 and NCR12224112 were initiated on 3/20/2018 due to "3pcs has tape gum on glass bead blast" and "tape gum staining and residue", respectively. Both nonconformances were found in the same work center (b) (4) . Between 9/13/2017 and 4/9/2018, your firm has initiated a total of (b) (4) NCRs and (b) (4) CCRs that contain the words "tape gum" in any of the "free cells."**

**Observation 6(A) Investigation and Response:**

On 02 Nov 2017, prior to the recent inspection, Zimmer Biomet opened CAPA CA-04031 (Attachment 1D-A, CAPA CA-04031, *Summary*) to improve the non-conforming product process at the Warsaw North Campus. After the inspection, Zimmer Biomet revised the scope of CA-

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

04031 to include the findings from Observations 1(D), 1(E), and 6. CA-04031 is currently in the Root Cause / Action Plan Phase and is due to be promoted to the Action Implementation Phase by (b) (4)

The Warsaw North Campus initiated the "Common Cause" nonconformance, or CCR, process in mid-September 2017 with the release of QM 13.1 Rev 5, "Control of Nonconforming Product" (Attachment 1D-B, *QM 13.1, Rev 5*, *Control of Nonconforming Product*), and SOP 13.1.1 Rev 3, "Nonconforming Product Procedure", (Attachment 1D-C, *SOP 13.1.1, Rev 3, Nonconforming Product Procedure*). The CCR process was first made available to a limited number of work cells and, since its initiation, Zimmer Biomet continues to expand the use of CCRs across the Warsaw North Campus. Although examples of CCRs are provided in section 7.9 of SOP 13.1.1 Rev 7 (Attachment 6A-A, *SOP 13.1.1, Rev 7, Nonconforming Product Procedure*), there is inconsistency in how operators apply this new process, as identified in the Observation. Currently, the decision about whether a nonconformance should result in a CCR versus an NCR rests with the initiator, and, per Section 7.7.3.3 of SOP 13.1.1 Rev 7, the CCR owner is responsible for opening an NCR if a nonconformance designated as a CCR does not meet the Common Cause nonconformance definition in section 7.9 of SOP 13.1.1 Rev 7. As an initial containment action, Zimmer Biomet conducted classroom training (Attachment 1E-B, *Training Evidence*) on QM 13.1 Rev 8 (Attachment 6A-B, *QM 13.1, Rev 8, Control of Nonconforming Product*) and SOP 13.1.1 Rev 7 (Attachment 6A-A) for NCR owners to reinforce the differences between a CCR and an NCR and the process for completing and closing the records.

In response to Observation 6(A) and to lessen future confusion about the proper assignment of CCRs and NCRs, Zimmer Biomet will revise (b) (4) Zimmer Biomet's electronic NCR system, to limit operators' capability to open nonconformance reports to CCRs only (Attachment 6A-C, *SOW1908657278*, *Statement of Work*). NCR/CCR Owners (i.e., Engineers/Technicians/Supervisors) will review the information in the CCR to determine whether the nonconformance requires the opening of an NCR instead. If so, the CCR will be closed and the system will automatically create an NCR with the same information to allow owners to complete the NCR investigation and any additional containment activities. This revision to the (b) (4) setting will also involve any necessary procedure updates, qualification activities, and user training. In addition, Zimmer Biomet will also update (b) (4) to include data entry rules that prevent certain Defect Codes from being used with CCRs and certain Cause Codes from being used with NCRs, to be consistent with the recently created INST 13.1.1.3 (Attachment 1E-D, *INST 13.1.1.3, Rev 1,* (b) (4) *NCR and CCR Defect Codes Definitions)*, which prohibits the use of certain CCR codes with NCRs and vice versa. This (b) (4) update will ensure that the system will not allow these types of incorrect coding.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 6A-1 | Updated CA-04031 to include Observation 6(A) findings regarding the appropriate use of CCRs and NCRs in the CAPA scope (Attachment 1D-A) | 11 May 2018 |
| 6A-2 | Conducted classroom refresher training on QM 13.1 Rev 8 and SOP 13.1.1 Rev 7 to reinforce the differences between CCRs and NCRs (Attachment 1E-B) | 11 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 6A-3 | Update (b) (4) to prevent operators from creating NCRs and to vest responsibility for the decision of whether a CCR or a NCR is required in the record owners | (b) (4) |
| 6A-4 | Revise QM 13.1 and SOP 13.1.1 to clarify the use of NCRs and CCRs and train personnel to the revisions | (b) (4) |
| 6A-5 | Update (b) (4) to include rules that prevent certain Defect Codes from being used with CCRs and certain Cause Codes from being used with NCRs | (b) (4) |
| 6A-6 | CAPA CA-04031 Root Cause / Action Plan Phase Complete | (b) (4) |
| 6A-7 | CAPA CA-04031 Action Implementation Plan Phase Complete | To be provided in a future response |
| 6A-8 | CAPA CA-04031 VOE Phase Complete | To be provided in a future response |

**FDA Observation 6(B)**

1. **Your firm inconsistently assigns defect codes based on the nonconformances documented in the NCR/CCR. For example,**

    1. **NCR12199179 was initiated due to "Tape gum on porous" on or around 12/18/2017. The NCR was assigned a defect code of "MA03-Foreign Material."**

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

2. **NCR12185478 was initiated due to "tape gum on the porous" on or around 10/18/2017. The NCR was assigned a defect code of "MA02-Defective Material."**

3. **CCR12217977 was initiated due to "Hair found in packaging," on or around 2/27/2018. The CCR was assigned a defect code of "MA02-Defective Material."**

4. **CCR12193114 was initiated due to "Hairs found inside blister packaging" on or around 11/24/2017. The CCR was assigned a defect code of "MA03-Foreign Material."**

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

On 02 Nov 2017, prior to the recent inspection, Zimmer Biomet opened CAPA CA-04031 (Attachment 1D-A, CAPA CA-04031, *Summary*) to improve the non-conforming product process at the Warsaw North Campus. After the inspection, Zimmer Biomet revised the scope of CA-04031 to include the findings from Observations 1(D), 1(E), and 6. CA-04031 is currently in the Root Cause / Action Plan Phase and is due to be promoted to the Action Implementation Phase by (b) (4)

Non-conformance records, both CCRs and NCRs, are documented in Warsaw North Campus's (b) (4) system. Currently, explanations of the various (b) (4) fields are included in WQLT003 Rev 3, "Procedure – (b) (4) NCR System Procedure" (Attachment 1E-A, *WQLT003, Rev 3, Procedure* – (b) (4) *NCR System Procedure*). Detailed information on Defect Codes and Cause Codes can be found in INST 13.0.1.2 Rev 4, "Nonconformance Code List" (Attachment 6B-A, *INST 13.0.1.2, Rev 4, Nonconformance Code List*). However, upon review of this Observation, Zimmer Biomet determined that, due to the identified inconsistency in the use of Defect Codes for NCRs and Cause Codes for CCRs, additional clarification regarding the definition and proper use of such codes is needed. Accordingly, Zimmer Biomet developed INST 13.1.1.3, (b) (4) NCR / CCR Defect Codes Definitions" (Attachment 1E-D, *INST 13.1.1.3, Rev 1,* (b) (4) *NCR and CCR Defect Codes Definitions)* to define all Defect Code and Cause Codes used in (b) (4) and to provide examples on when to use each. Zimmer Biomet has completed instructor-led training was provided to the top (b) (4) , of the (b) (4) owners (Attachment 1E-B, *Training Evidence*). The remaining (b) (4) % of (b) (4) owners will be trained as well, and documentation of that training will be submitted in the first update to this response.

The procedural revisions will ensure that, going forward, any new CCRs and NCRs have consistent defect and cause coding. To ensure that the deficiencies in coding did not mask

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

important product or patient safety risks that would have been identified by CCR and NCR trending if the records had been properly coded, Zimmer Biomet will remediate the coding of a sample of NCRs and CCRs and perform retrospective trending using the remediated files. Specifically, Zimmer Biomet will remediate (b) (4) records created in (b) (4) and, based on the remediated records, create updated trend charts. Zimmer Biomet will compare the post-remediation trend charts with the previously prepared trending results (b) (4). If the post-remediation trending data does not trigger a different result than the one previously reached in the (b) (4), then Zimmer Biomet can conclude that the gaps in coding did not affect the CCR and NCR trends and thus that no further remediation would be warranted. If, on the other hand, a different result is reached, then Zimmer Biomet will expand the remediation of CCR and NCR records to all records created (b) (4), which accounts for (b) (4) (b) (4) records.

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 6B-1 | Updated CA-04031 to include Observation 6(B) in its scope (Attachment 1D-A) | 11 May 2018 |
| 6B-2 | Created INST 13.1.1.3, which provides additional Defect Code (and Cause Code) clarifications (Attachment 1E-D) | 11 May 2018 |
| 6B-3 | Trained the top (b) (4) % of (b) (4) owners, (b) (4), to new INST 13.1.1.3 (Attachment 1E-B) | 11 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 6B-4 | Complete training to INST 13.1.1.3 to the remaining, (b) (4) (b) (4) (b) (4) users | (b) (4) |
| 6B-5 | CAPA CA-04031 Root Cause /Action Plan Phase Complete | (b) (4) |
| 6B-6 | CAPA CA-04031 Action Implementation Phase Complete | To be provided in a future response |
| 6B-7 | Remediate (b) (4) CCR and NCR records from March 2018 to correct CCR versus NCR inconsistencies, update any Defect and Cause Codes, and add multiple codes if needed | To be provided in a future response |
| 6B-8 | Conduct retrospective trending of the remediated CCR and NCR records and compare the results to the CCR and NCR | To be provided in a future response |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| | | |
|---|---|---|
| | trending results reviewed in the March 2018 CAPA review | |
| 6B-9 | If required by the outcome of Action 3, remediate and conduct a retrospective review of (b) (4) Records created since October to correct CCR versus NCR inconsistencies, update any Defect and Cause Codes, and add multiple Codes, if needed | To be provided in a future response |
| 6B-10 | CAPA CA-04031 VOE Phase Complete | To be provided in a future response |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 7

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 7**

**Procedures for acceptance activities have not been adequately established.**

***This is a repeat observation from the FDA inspection dated 9/12/2016 to 11/22/2016.***

**Specifically,**

**You do not have a documented rationale to support acceptance criteria defined in your in-process packaging seal inspection procedure I00051.3, version 2, which allows up to (b) (4) particles (b) (4) in sterile package seals or why "red" or particles (b) (4) are un-acceptable.**

**Observation 7 Investigation and Response:**

On 04 May 2018, Zimmer Biomet initiated CAPA CA-04508 (Attachment 7-A, CAPA CA-04508, *Summary*) to address the issue identified in Observation 7 concerning lack of a documented rationale to support acceptance criteria defined in process packaging seal inspection procedure I00051.3, version 2. Initial correction and containment have been already addressed and the CAPA has been promoted from the correction/containment phase. CAPA CA-04508 is currently in the Root Cause / Action Plan phase and is due to be promoted to the Implementation phase by (b) (4). This CAPA will evaluate and document rationales for (b) (4) sterile package inspection criteria (e.g., allowable particulates) and will revise acceptance criteria if necessary.

As part of the standard manufacturing process, 100% of sterile packages are inspected for all foreign material per inspection criteria I00051.3, version 2. Inspection criteria I00051.3, version 2 prohibits any hair, moisture, or smudge within the package, but allows up to (b) (4) particles (b) (4) and does not allow particles (b) in size or any "red particles," regardless of size, in sterile package seals but the rationale for accepting or rejecting packaging seals based on particles is not provided I00051.3. Zimmer Biomet is investigating the rationale under CAPA CA-04508.

In assessing this issue, Zimmer Biomet considered the potential impact of particles smaller than (b) on seal integrity, seal strength, and product contamination. Currently, all validation, process monitoring, bioburden, and sterilization packaging samples use the current inspection criteria. Zimmer Biomet has initially determined that no immediate modification of the specification or containment actions are required, as described further in this response.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Related to seal performance, Zimmer Biomet uses a conservative approach of product testing for both monitoring and product release. This approach includes testing the actual sealed product for (b) (4). Any impact of embedded particulate on the sterile barrier integrity would have been captured in our process monitoring data. All our current data supports the validity of this long-standing process specification. Moreover, Zimmer Biomet has detailed, long-term, shelf life data for which samples were accepted under inspection criteria I00051.3. No failures during shelf-life testing have been attributable to embedded particulates that fell within the acceptance criteria of I00051.3.

Although particulates embedded in the sterile barrier seal are unlikely to cause product contamination due to their adhesion in the sterile seal, Zimmer Biomet also considered this potential consequence in evaluating this Observation. Zimmer Biomet's cleaning validation and process monitoring samples are (b) (4) tested to GES09802 "Global Engineering Specification for Implant Residual Materials and Endotoxin Limits". This finished product specification, including sterile packaging, contains unambiguous acceptance criteria for product cleanliness, including debris. The specification defines limits for residual materials, debris, bacterial endotoxin, and cytotoxicity for implantable products. Particulates which are encapsulated and released from the sterile barrier seals would be captured as part of this testing as it relates to a toxicity reaction due to excessive contamination. Lastly, Zimmer Biomet conducts bioburden evaluation on (b) (4) sterilized, (b) (4) sterilized, and (b) (4) sterilized product families on a (b) (4) basis to ensure consistent bioburden within-specification levels and an (b) (4) Impact of particulates encapsulated in the sterile barrier seals and their effect on sterilization effectiveness would inherently be evaluated as part of this testing. Results of contamination, sterilization, and bioburden testing do not show a product safety or performance impact attributable to the inclusion of small particulates within the sterile barrier seal.

Thus, all current data from validations, process monitoring, and shelf-life testing confirms that the acceptance criteria of the (b) (4) specification does not pose patient risk. No immediate modifications of the specification or containment actions are required.

As described above, Zimmer Biomet initiated CAPA CA-04508 to further investigate and document the rationale for the acceptance criteria for particles in the packaging seal inspection procedure.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 7-1 | Initiated CAPA CA-04508 to evaluate and address the finding regarding the lack of a documented rationale for acceptance criteria for packaging visual inspections (Attachment 7-A) | 04 May 2018 |
| 7-2 | Completed CAPA CA-04508 Correction / Containment Phase | 10 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 7-3 | CAPA CA-04508 Root Cause / Action Plan Phase Complete | (b) (4) |
| 7-4 | CAPA CA-04508 Action Implementation Phase Complete | To be provided in a future response |
| 7-5 | Documented rationale for the acceptance criteria for particles in sterile barrier seals in I00051.3 | To be provided in a future response |
| 7-6 | CAPA CA-04508 VOE Phase Complete | To be provided in a future response |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 8

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 8**

**Procedures for training and identifying training needs have not been established.**

**Specifically,**

**Your firm's training procedures SOP 18.0.1, rev 12, "Training Identification and Documentation," effective 27-Mar-18 and QM 18.0, rev. 8, "Training," effective 27-Mar-2018, do not ensure that all employees are adequately trained. For example,**

A. **Your firm's operators were unable to identify procedures related to their operations and did not perform operations per your firm's work instructions. During a walkthrough in the (b) (4) manual cleaning area on 04/09/2018, an employee was unable to identify what the process specification referenced for a step of manual cleaning referenced in section 11, step (b) (4) of WCLN017, (b) (4) (b) (4) ," Revision 1. Another employee in your (b) (4) cleaning area on 04/09/2018 was unable to locate the procedure used for cleaning your (b) (4) after manually cleaning the product. Additionally, this employee stated they were on step (b) (4) of section 11 in WCLN017, but had already (b) (4) from the product, which is meant to remain on the product until step (b) (4) Additionally, they were not using a wire brush to remove debris, as stated in step (b) (4) but a nylon brush, as is described in step (b) (4) There was no wire brush observed at their station. They stated they use a nylon brush, instead of a wire brush, as the wire brush can scratch the polished surfaces. The polished surface was previously covered (b) (4) .**

B. **During a second walkthrough of the facility on 04/17/2018, an operator was observed measuring part (b) (4) for specification (b) (4) as part of their line clearance activities. According to specification (b) (4) -DWG-1 Rev. B, specification (b) (4) upper limit should measure (b) (4) with a tolerance of (b) (4) . Your operator measured this specification (b) (4) for the first part as (b) (4) and the second part as (b) (4) and stated the part was "good." These measurements were not identified as non-conformances until the operator was directly asked what the specification was and if the parts were conforming.**

C. **On 4/9/2018, your firm's employee in packaging, used a (b) (4) gauge to measure the tray seal in the (b) (4) packaging area. Your firm's "Package Requirements" states that the narrowest seal width for "Seal Width-Trays" is "not less than (b) (4) ." Your employee stated that the only gauge at her station was the (b) (4) " gauge.**

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**D. During an inspection of the sterile sealing process with asset number (b) (4) on 4/9/2018, the sealer operator did not properly demonstrate how to measure seal width using a gauge per procedure 100051.3, version 2. The operator incorrectly measured an area outside of the blister package seal.**

**E. On 4/9/2018, and operator manufacturing part number (b) (4) (b) (4) ) using automated diameter system referred to the (b) (4) limits for the product specifications (b) (4) ) and not the correct tolerances of (b) (4) mm. Therefore, there is a subset of measurements which could be non-conforming and not captured or entered into the firm's non-conforming database.**

**Observation 8 Investigation and Response:**

On 14 Dec 2016, Zimmer Biomet opened CAPA CA-03127 during the previous FDA inspection of the Warsaw North Campus to address several opportunities for improvement to the training system that had been identified during the inspection and to ensure the implementation of a robust site-level training program. Zimmer Biomet has determined that the findings in Observation 8 fall under this existing CAPA and, on 5/10/2018, Zimmer Biomet revised the scope of CA-03127 to include Observation 8. (Attachment 8-A, CAPA CA-03127*, Summary*). CA-03127 is currently in in the Action Implementation Phase and is due to be promoted to the Action Implementation Approval Phase by (b) (4) .

Zimmer Biomet plans to substantially revise its operator training program to address the apparent training deficiencies identified in this Observation. Under CA-03127, Zimmer Biomet plans to implement a (b) (4) that requires operators' demonstration of capability prior to performing their work functions. (b) (4) In addition, Zimmer Biomet intends to increase the accessibility of required manufacturing process documentation across the Warsaw North Campus manufacturing facility and to develop and implement a site-wide training program reinforcing the importance of adhering to procedures and work instructions and not making unauthorized process changes, both to address the findings in Observation 8(A). Finally, Zimmer Biomet intends to implement an internal Layered Process Audit (LPA) program at the site by which management personnel will visit the manufacturing floor on a periodic and unannounced basis to audit manufacturing processes. In addition to providing additional control of and insight to day-to-day manufacturing operations, the LPAs will also serve to increase operators' experience in responding to audit and inspection inquiries.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

In addition to the systemic corrective action described above, during the recent inspection and immediately following the receipt of the FDA-483, Zimmer Biomet took several correction steps to investigate and address the specific findings in the Observation regarding employees exhibiting inadequate training. Each of the employees referenced in the Observation's examples had previously undergone training, so Zimmer Biomet sought to determine whether that training had been ineffective or if other factors contributed to the employee's misstatements. Each specific example is addressed below:

- Observation 8(A): Zimmer Biomet took immediate action to address the finding that an operator was unable to identify or locate work instructions and performed cleaning steps out of order and with the wrong tool. Zimmer Biomet required the operator to demonstrate their ability to identify specifications, locate procedures, and complete steps in order. (Attachment 8-B, *Correction 1*). Zimmer Biomet will also be increasing the accessibility of required manufacturing process documentation within the (b) (4) cleaning area by issuing binders to the impacted workstation. Zimmer Biomet will also train the (b) (4) cleaning team on the importance of not deviating from the ordered steps in work instructions and procedures and not otherwise making unauthorized process changes. Finally, Zimmer Biomet issued a metal brush to the (b) (4) cleaning station to replace the incorrect nylon brush. (Attachment 8-C, *Correction 4*).

- Observation 8(B): To address the finding that an operator did not properly identify non-conforming parts, Zimmer Biomet required the operator to demonstrate ability to perform proper line clearance activities, including the measurement and acceptance defined within specification (b) (4) . The operator confirmed that she fully understood the line clearance process and would not incorrectly accept nonconforming parts. (Attachment 8-D, *Correction 5*).

- Observation 8(C): Zimmer Biomet issued the appropriate (b) (4)" gage to the (b) (4) packaging work area as a replacement for the incorrect (b) (4) gage. (Attachment 8-E, *Correction 6*). Metrology will review its practices to ensure that correct gages and other tooling are available at point of use, as discussed further in the response to Observation 11.

- Observations 8(D) and (E): Zimmer Biomet is following up with the operators identified in the last two examples in the Observation to further investigate and discuss their reported errors. Both operators reported being nervous about being questioned by the FDA Investigators, which resulted in their forgetting the process steps and making mistakes in responding to the Investigators' questions. Zimmer Biomet is determining if

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

both operators did know how to properly conduct the activities about which they were questioned.

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 8-1 | Revised the scope of CA-03127 to include the findings in Observation 8 regarding employee training (Attachment 8-A) | 10 May 2018 |
| 8-2 | Confirmed the ability of operators cited in Observation 1(A) to identify specifications, locate procedures, and complete steps in order (Attachment 8-B) | 10 May 2018 |
| 8-3 | Confirmed that the operator cited in Observation 8(B) fully understood the line clearance process and would not incorrectly accept nonconforming parts (Attachment 8-D) | 10 May 2018 |
| 8-4 | Issued the appropriate (b) (4)" gage to the (b) (4) packaging work area (Attachment 8-E) | 10 May 2018 |
| 8-5 | Issued a metal brush to the (b) (4) cleaning station to replace the incorrect nylon brush (Attachment 8-C) | 10 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 8-6 | Confirm that the operators cited in Observations 8(D) and (E) do know how to properly conduct the activities about which they were questioned | (b) (4) |
| 8-7 | Increase accessibility of required manufacturing process documentation within the (b) (4) clean area. | (b) (4) |
| 8-8 | Train the (b) (4) cleaning team on the importance following work instructions and procedures | (b) (4) |
| 8-9 | Complete (b) (4) that requires operators' demonstration of capability prior to performing their work functions | (b) (4) |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

| | | |
|---|---|---|
| 8-10 | Increase the accessibility of required manufacturing process documentation across the Warsaw North Campus manufacturing facility | (b) (4) |
| 8-11 | Develop and implement a site-wide training program reinforcing the importance of adhering to procedures and work instructions and not making unauthorized process changes | (b) (4) |
| 8-12 | Implement an internal Layered Process Audit (LPA) program at Warsaw North Campus | (b) (4) |
| 8-13 | CAPA CA-03127 Action Implementation Phase Complete | (b) (4) |
| 8-14 | Implement a (b) (4) that requires operators' demonstration of capability prior to performing their work functions | (b) (4) |
| 8-15 | CAPA CA-03127 VOE Phase Complete | (b) (4) |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 9

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 9**

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

***This is a repeat observation from the FDA inspection dated 9/12/2016 to 11/22/2016.***

**Specifically,**

**SOP 28.0.3: Sterile Packaging Sealer Monitoring (Rev. 5, effective 1/26/2018) requires periodic monitoring of packaging seal strength and integrity. It states "**(b) (4)

**Though not clearly stated in the procedure, your firm's Vice President of Quality Assurance stated it was intended to require seal strength and integrity testing to be performed on samples from both the** (b) (4) **and** (b) (4) **. However, you were unable to provide objective evidence that this process is followed because traceability between test samples and** (b) (4) **is not documented.**

**Furthermore, on 4/11/2018, your firm's Quality Technician stated he performs seal integrity testing only on samples from the** (b) (4) **the run and seal strength testing only on samples taken at the** (b) (4) **of the run.**

**Notably, your firm relies on such process monitoring as justification for continuing to package devices using sealers whose process validations are known to be inadequate.**

**Observation 9 Investigation and Response:**

On 15 Dec 2018, prior to the April 2018 Warsaw North Campus FDA Inspection, Zimmer Biomet opened CAPA CA-04129 (Attachment 9-A, CAPA CA-04129, *Summary*) to address Sealer Process Monitoring testing errors identified through a process monitoring failure investigation. This CAPA was updated on 02 May 2018 to include the specific issue identified in the Observation regarding the process for testing seal strength and integrity and other related activities. This CAPA is currently in the Action Implementation phase and is scheduled to be promoted to the Verification of Effectiveness phase by (b) (4) .

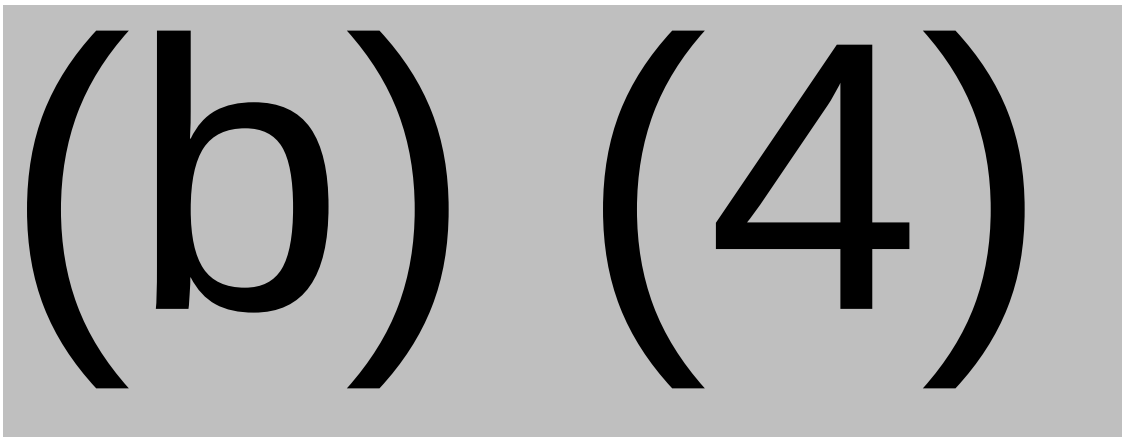
Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Zimmer Biomet investigated the findings in this Observation by interviewing the involved Quality Assurance Technicians on 12 Apr 2018. Through that process, Zimmer Biomet determined that there were technicians on the (b) (4) and (b) (4) shifts not following the sampling portion of the procedure due to a gap in their training. On the other hand, (b) (4) shift technicians confirmed they conducted sampling per procedure. As a result of this investigation, immediate action was taken to informally retrain all related Quality Assurance Technicians on the proper sampling and testing for SOP 28.0.3, Rev 5, Sealer Process Monitoring.

Also as a part of immediate correction and containment activities, Zimmer Biomet performed a detailed review of SOP 28.0.3, Rev 5. The review identified a need for further clarification of the procedure to improve Operations team member and Quality Assurance Technician understanding of process monitoring requirements, including sampling and sample traceability. The changes to the SOP included clarifying what testing should be completed at the (b) (4) and (b) (4) of (b) (4) and additional requirements for tracing of samples pulled for monitoring purposes. SOP 28.0.3 was updated and released on 24 Apr 2018 (Attachment 9-B, *SOP 28.0.3, Rev 6, Sterile Packaging Sealer Monitoring*). Associated with this SOP revision, Quality Assurance Technicians and others involved in sealer process monitoring were trained to updates in the revised version of SOP 28.0.3 (Attachment 9-C, *Training Records for SOP 28.0.3, Rev 6, Sterile Packaging Sealer Monitoring*).

As a result of the 2016 FDA inspection of the Warsaw North Campus, significant increases in packaging process monitoring were implemented to reduce the risks of non-conformances and of release of nonconforming product during the ongoing, comprehensive, remediation activities under (b) (4). Through this increased process monitoring, an average of (b) (4) samples are tested (b) (4) covering all packaging configurations on all packaging processes. The following is a summary of sealer process monitoring data compiled since additional process monitoring was implemented.

**Warsaw North Campus Sealer Process Monitoring (26 Sep 2016 - 30 April 2018)**



Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

(b) (4) additional investigations concluded (b) (4)

The North Campus sealer summary above shows the robust nature and capability of the sealer processes. It also confirms that, despite variability in our sample selection by some technicians, there is an extremely low likelihood of these processes resulting in packaging defects and an even lower chance that any defects caused by potential process would escape detection during monitoring and acceptance activities. Analysis of the monitoring failure data did not show significant variation or trends in the data related to in-lot variation or run-to-run variation that would suggest the anomalies in sample timing affected the robustness of the monitoring. The confidence and reliability associated with these processes exceeds our (b) (4) % confidence and (b) (4) % reliability acceptance levels for high risk processes per Corporate Procedure CP09505, Sample Plans - Process Validation *(*Attachment 9-D, *CP09505, Rev 2, Sample Plans – Process Validation*).

In each case of a specification failure, per SOP 28.0.3, Zimmer Biomet performed a full investigation in accordance to Corporate Procedure CP07001, Issue Evaluation. For each investigation, all in scope product was contained internally during the duration of the investigation. This investigation process provides an extremely high confidence that no non-conforming product was distributed. In addition, please note that (b) (4) legacy sealers have been removed from production between (b) (4) due to process improvements, equipment-type consolidation, or remediation activities, further improving the packaging process at the Warsaw North Campus. In total, (b) (4) % of sealers in scope for (b) (4) (b) (4) have been removed and/or replaced through revalidation to current standards as of 11 May 2018.

Due to the volume of data collected, and the high capability of the subject sealing processes, Zimmer Biomet has determined that no additional containment is required. Also, per the investigation and data analysis, Zimmer Biomet further determined that the method of sampling and lack of traceability has not impacted the ability to identify specification failures or the need to remove sealers under interim controls, pending validation remediation, from production processes at Warsaw North Campus. Further, the data analysis confirms Zimmer Biomet's ability to identify process drift, even if samples were tested at the incorrect time, because the sampling will nevertheless signal when we have nonconforming product that could have occurred through a shift in the production process. Further potentially related Corrective Actions will be investigated per CAPA CA-04129.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 9-1 | Updated SOP 28.0.3 (rev 6) via change request MC191458 to clarify that:<br>• Samples from the (b) (4) of the s(b) (4) should be in a bag/container designating them as (b) (4) (b) (4) samples.<br>• Samples from the (b) (4) of the (b) (4) and from the (b) (4) of the (b) (4) shall be represented within each test method.<br>(Attachment 9-B) | 24 Apr 2018 |
| 9-2 | Updated CA-04129 to include the finding from Observation 9 regarding incorrect sampling technique for packaging process monitoring (Attachment 9-A) | 02 May 2018 |
| 9-3 | Trained Quality Assurance Technicians and others involved in sealer process monitoring to revised SOP 28.0.3 (Attachment 9-C) | 10 May 2018 |

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 9-4 | Revise SOP 28.0.3 to further clarify how packaging process monitoring samples should be distributed between applicable test methods and train personnel to the revisions | (b) (4) |
| 9-5 | CAPA CA-04129 Action Implementation Phase Complete | (b) (4) |
| 9-6 | CAPA CA-04129 VOE Phase Complete | (b) (4) |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 10

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 10**

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

***This is a repeat observation from the FDA inspection dated 9/12/2016 to 11/22/2016.***

**Specifically,**

**Process controls for packaging sealer Asset (b) (4) have not been adequately established.**

**The *Heat Sealing Parameter Sheet (HSPS)* for Asset (b) (4) (Rev. 4, effective 3/22/2018) specifies the pressure setting as "NA". The respective process validation (Validation Report #487) stated that pressure is "not considered critical" because it is "fixed on the machine and cannot be changed." However, the Operating Instructions manual for the sealer explains:**

- **E. Contact pressure may be adjusted by positioning the (b) (4) and adjusting it using an (b) (4) .**
- **F. Pressure may be read-out using the sealer (b) (4) " function.**
- **G. The (b) (4) " function "should be performed before the (b) (4) working process and should be documented by filing the print out."**
- **H. Too low of pressure could result in a seal that "does not hold", which may be remedied by readjusting the pressure of the (b) (4) .**

**The (b) (4) function is not mentioned in *WEQP168: Work Instructions, Packaging – Auto- Sterile Sealing Machines (*Rev. 4, effective 4/9/2018) or *QM 9.7: Manufacturing Equipment Maintenance (*Rev. 22, effective 11/28/2017). Interviews with an operator on 4/10/2018 and maintenance personnel on 4/11/2018 revealed the (b) (4) function is not used.**

**Asset (b) (4) is one of (b) (4) sealers used since the previous FDA inspection. The other (b) (4) were removed from service (b) (4) .**

**Observation 10 Investigation and Response:**

Zimmer Biomet respectfully disagrees with the finding that the "process controls for packaging sealer Asset (b) (4) have not been adequately established." Zimmer Biomet had necessary process controls in place to ensure that the sealer at issue, Asset (b) (4) conformed to Zimmer Biomet's established specifications. We note that Asset (b) (4) was been removed

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

from production use (b) (4), according to a pre-inspection obsolescence plan. (Attachment 10-A, *Work Order Number* (b) (4)).

In accordance with 21 C.F.R. 820.70 and 820.75, Zimmer Biomet had performed a validation of asset (b) (4) (Sealer (b) (4)) in June 2015, and established appropriate process control and monitoring, prior to its first use. As a part of this validation, Zimmer Biomet determined that the pressure setting referred to in the observation was not a critical parameter that required independent monitoring. This determination was based on the limitations of the equipment, specifically, that it did not have a feature that allowed operators to set pressure and there was no quantitative pressure monitoring function. It should be noted that guidance for sterile barrier systems published by (b) (4) (the manufacturing of the packaging material) clearly indicates that for most heat seal materials, pressure is the least significant of the three factors required to make a heat seal. This is further supported by the results of actual seal strength and integrity testing showing very robust product performance from this sealer with no failures noted, despite the fact that pressure was not controlled as a critical parameter. See detailed monitoring data later in the response to this Observation.

Instead of independently monitoring the pressure setting, Zimmer Biomet used a combination of (b) (4) (b) (4) ) and (b) (4) ((b) (4) ) to ensure the on-going validated state of the sealer and continuous product conformance to specifications. Where possible, direct measurement of (b) (4) and (b) (4) is the clearest indicator of ongoing process performance. It should be noted that under (b) (4) sealer (b) (4) was subject to a triage review as per SOP 9.4.17 "Process Validation Triage Review" (Attachment 10-B, *SOP 9.4.17, Rev 2, Process Validation Triage Review*). This review assessed whether the process was being executed per the original validated process parameters and whether monitoring signals suggested the process was producing non-conformances at a rate higher than expected. This review showed no issues with the operation of this process historically.

Zimmer Biomet acknowledges that the equipment manual that states the contact pressure may be adjusted (at the time of maintenance) by positioning of the (b) (4) and adjusting the (b) (4) as cited in the Observation. However, this process is manual, very subjective and provides only gross adjustment of the contact pressure. Further, Zimmer Biomet contacted the manufacturer of the sealing equipment to verify whether the contact pressure can be validated, and the response from the manufacturer indicate that the (b) (4) function described in the Observation is only intended to verify the contact pressure of the (b) (4) when aligned for surveillance due to wear and tear and not to provide quantitative sealing pressure for the purposes of process monitoring. These factors make practical use of pressure

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

as an in-process control method unreliable and unfeasible for Sealer (b) (4) and other (b) (4) (b) (4) sealers. For these reasons, when validating the (b) (4) - (b) (4) sealers, including Sealer (b) (4) Zimmer Biomet intentionally omitted the (b) (4) function from the validation and process monitoring, as described above. Zimmer Biomet is under no obligation to use all features offered by a given piece of equipment or described in its User Manual; the company is only required to validate the equipment's features that it intends to use. Thus, Zimmer Biomet's choice to forego use of the (b) (4) function does not mean that the sealers were not properly validated or that they were not subject to adequate process controls or process monitoring.

Zimmer Biomet uses a very conservative monitoring approach that involves testing the actual sealed product for (b) (4) and visual inspection to ensure conformity to packaging specifications. **Table 1** provides an overview of monitoring data collected between 30 Sep 2016 and 18 Apr 2018 for sealer asset (b) (4).

(b) (4)

All monitoring samples passed the (b) (4), and visual inspection. A basic approximation of the confidence and reliability of this process using the binomial distribution suggests a (b) (4)% confidence that the percent of conforming product from this process exceeds (b) (4)%. This is higher than current process validation requirements for new sealers based on CP09505 "*Sample Plans - Process Validation*" (Attachment 10-C, *CP09505, Rev 2, Sample Plans - Process Validation*). Based on this data, Zimmer Biomet has determined that no containment or field action related to sealer asset (b) (4) is required.

Zimmer Biomet takes FDA's observations and comments seriously regarding process controls and, after the 2016 inspection, initiated CAPA CA-02380 (Attachment 10-D, CAPA CA-02380, *Summary*) to investigate and evaluate the observations 1(C)(i), 3(F), and 6(A) from the 2016 FDA-483 regarding process controls. As part of CAPA CA-02380 and the (b) (4) remediation program, Zimmer Biomet has implemented two significant interim controls to ensure that packaging sealers operate in a state of control while corrective actions and planned obsolescence are implemented. Zimmer Biomet implemented IC-019, "*Sterile Packaging Sealer Increased Monitoring Interim Control*," (Attachment 10-E, *IC 019, Rev 1-8 , Sterile Packaging*

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

*Sealer Increased Monitoring Interim Control*), which has now been superseded by permanent SOP 28.0.3, "*Sterile Packaging Sealer Monitoring*" (Attachment 10-F, *SOP 28.0.3, Rev 6, Sterile Packaging Sealer Monitoring*). Zimmer Biomet also implemented interim control IC-014, "*Process Validation Interim Control*" (Attachment 10-G, *IC-014, Rev 1-6, Process Validation Interim Control*) to develop packaging process validation and to define the process for ongoing testing for all packaging sealers. This IC has now been superseded by SOP095200, "*Process Validation*" (Attachment 10-H, *SOP095200, Rev 1, Process Validation*). As part of (b) (4) (b) (4) all packaging processes and sealers have been remediated to comply with IC-014 and are also currently being remediated to SOP095200.

As a preventive measure, Zimmer Biomet plans to investigate if there are any legacy packaging sealers, currently used in production, under interim controls, which specifies pressure settings as "N/A" in their corresponding Heat Sealing Parameter Sheets (HSPS) to determine if further control may be necessary. Zimmer Biomet plans to evaluate the need to add a (b) (4) (b) (4) step during the normal preventive maintenance of the sealers. An action item task will be added to CAPA CA-02380 to address the investigation activity.

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 10-1 | Investigate whether any legacy packaging sealers currently used in production specify pressure settings as (b) (4) in their HSPSs and may require further action | (b) (4) |
| 10-2 | Evaluate the need to add a (b) (4) verification step to preventive maintenance for sealers | (b) (4) |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

# FDA Observation 11

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**FDA Observation 11**

**Procedures to ensure equipment is routinely calibrated, inspected, checked and maintained have not been adequately established.**

**Specifically,**

**The preventive maintenance plan for packaging sealer Asset (b) (4) requires to "ENSURE THAT DISTANCE BETWEEN SEALING DIES IS (b) (4) MM" on an (b) (4) basis. On 4/11/2018, your firm's Maintenance Technician stated he used a (b) (4) gage to verify the distance of (b) (4) mm during the most recent (b) (4) maintenance on 5/8/2017. The (b) (4) gage is not tracked or calibrated by your firm's metrology department. He said he had used the gage since being hired in 1997. On 4/11/2018, we observed the gage to appear visibly corroded and damaged.**

***QM 11.0: Control of Inspection, Measuring, and Test Equipment* (Rev. 8) requires that "Measurement and the test equipment shall be identified with a unique identification number and the calibration due date" and "The quality department shall maintain an electronic real-time calibration schedule by gage number".**

**The Operating instructions manual for packaging sealer Asset (b) (4) states that too great a distance between sealing dies could result in a seal that "does not hold".**

**Observation 11 Investigation and Response:**

Zimmer Biomet has initiated CAPA CA-04510 (Attachment 11-A, CAPA CA-04510, *Summary*) to address the issues identified in Observation 11 concerning the use of an uncalibrated gage. CAPA CA-04510 currently is in the Root Cause Phase and is scheduled to promote on (b) (4) (b) (4).

Zimmer Biomet manufacturing personnel are required by procedure (Attachment 11-B, *QM 11.0, Rev 9, Control of Inspection, Measuring, and Test Equipment*) and trained to check and record calibration information for all gages prior to use. The (b) (4) gage cited in the FDA observation was used by one maintenance technician for routine maintenance on a single noncritical feature on one packaging sealer. This gage was not ever used to accept product.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

Upon becoming aware of the use of this gage, Zimmer Biomet removed the (b) (4) gage in question and it was taken to the metrology lab for quarantine. The (b) (4) gage, per calibration procedures, was assigned a unique identification number, (b) (4) (Attachment 11-C, (b) (4) *Record for* (b) (4) ), and entered into the calibration database solely for the purpose of tracking the result of the subsequent calibration check. On 12 Apr 2018 (b) (4) gage (b) (4) was verified internally and found to be within calibration specifications. In an effort to increase confidence in this result, the gage was also sent to an approved (b) (4) (b) (4) ) for verification. Again, the gage came back as being within calibration specifications. Based on these verification results Zimmer Biomet confirmed that there was no impact to final product and no further containment actions were necessary. This gage has subsequently been removed from use.

As a further containment/correction activity, a meeting was held with all of the maintenance personnel to address the potential inappropriate use of personal gages that are not part of the formal equipment management program. All maintenance personnel were instructed to immediately cease the use of any personal gages, send any personal gages to the calibration department for calibration verification and then remove them from the company premises. Maintenance personnel were instructed that only calibrated, company owned gages are to be used. Zimmer Biomet has self-identified (b) (4) gages used in the facility, and as such, the elimination of (b) (4) gages is in the scope of the (b) (4) Calibration Work stream, which is scheduled to be completed in (b) (4) . In addition, Zimmer Biomet audited the entire Warsaw North Campus manufacturing facility, including equipment maintenance operations, and no additional uncalibrated gages were discovered or surrendered by personnel. (Attachment 11-D, *Meeting with Maintenance use of* (b) (4) *Gages*). Checking for undocumented, uncalibrated gages has been confirmed to be on the focused audit process (the (b) (4) Inspection Process) to ensure ongoing compliance. (Attachment 11-E, *Walk-Through Audit Check-Sheet*).

Since January, 2017, (b) (4) separate rounds of Manufacturing Cell Audits have been conducted on the Zimmer Biomet north campus. The scope of these audits included all of the (b) (4) manufacturing cells. These audits were completed using INST 17.0.1.9, Walk Through Audit Check Sheet (Attachment 11-E) in which calibration status is included.

Additionally, Quality Management System (QMS) audits were conducted (b) (4) (b) (4) (b) (4) (b) (4) audits included gages and calibration.

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Completed Actions:**

| No. | Action | Completion Date |
|---|---|---|
| 11-1 | Quarantined the employee's (b) (4) gage in the metrology lab and added the gage to the (b) (4) database (as gage (b) (4) ) to facilitate a calibration check (Attachment 11-F, *Equipment Profile* (b) (4) ) | 12 Apr 2018 |
| 11-2 | Performed calibration check of (b) (4) at Zimmer Biomet and found the gage to be within calibration specifications (Attachment 11-C) | 12 Apr 2018 |
| 11-3 | Created Issue Evaluation IE-04852 to investigate and evaluate potential impact of the use of gage (b) (4) IE-04852 triggered initiation of CAPA CA-04510. (Attachment 11-G) | 17 Apr 2018 |
| 11-4 | Completed GRN C1002026 for corrosion/damage on (b) (4) (b) (4) Result of GRN C1002026 documented that corrosion/damage had no impact to dimensional results or impact on gage use. (Attachment 11-H) | 02 May 2018 |
| 11-5 | Opened CAPA CA-04510 to evaluate and address the findings in Observation 11 (Attachment 11-A) | 04 May 2018 |
| 11-6 | Held meeting with all maintenance personnel to reinforce the prohibition on the use of (b) (4) gages (Attachment 11-D) | 12 Apr 2018 |
| 11-7 | Audited the Warsaw North Manufacturing facility and confirmed that no additional (b) (4) gages were in use by personnel (Attachment 11-D) | 12 Apr 2018 |
| 11-8 | Confirmed a check for undocumented, uncalibrated gages on the focused audit process (Attachment 11-E) | 13 Apr 2018 |
| 11-9 | Update QM11.0 to remove references to personal gages and clarify the requirement that gage calibration status must be verified prior to each use. (Attachment 11-B) | 10 May 2018 |

Zimmer Biomet
56 E. Bell Dr.
Warsaw, IN 46582
574.267.6131
www.zimmerbiomet.com

**Planned Actions:**

| No. | Action | Estimated Completion Date |
|---|---|---|
| 11-10 | Complete CAPA CA-04510 Correction Phase | 10 May 2018 |
| 11-11 | Evaluate potential procedural changes to existing maintenance procedures to require documentation of the gage number and calibration status during the completion of maintenance work orders. | 13 Jul 2018 |
| 11-12 | Evaluate potential procedural changes regarding the issuance of proper gages to complete the required job across the Warsaw North Campus (cross-reference Observation 8(C)) | 13 Jul 2018 |
| 11-13 | Complete CAPA CA-04510 Root Cause Phase | 27 Jul 2018 |
| 11-14 | Complete CAPA CA-04510 Action Implementation Phase | To be provided in a future response |
| 11-15 | CAPA CA-04510 VOE Complete | To be provided in a future response |