Validation Machine Process of "Crosslink, Low Profile Break-off" On Tornos Deco 20

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Abstract *— The United States (U.S.) medical device manufacturing sector is a highly diversified industry that produces a range of products designed to diagnose and treat patients in healthcare systems worldwide. Process validation is an essential part of medical device manufacturing. As an objective of this project there should be the completion of an operational qualification (OQ) to tests the process produces a consistent product that meet with the design specs and the qualification protocol (PQ) examines the capabilities of the current process in producing a safe, high-quality product under simulated conditions of Crosslink Low Profile Break-off. After the qualifications runs the data will be gather to analyze if the data follows a Normal Distribution, then will be calculate the Tolerance Intervals, the ANOVA's, Capabilities, Sampling Size and the Control Limits for each of the critical dimensions.*

Key Terms *— Control Limits, Operational Qualification, Performance Qualification, Validation, Low Profile Crosslink, Spinal.*

INTRODUCTION

The medical device industry is a highly regulated sector of the economy, and regulatory environments, both at home and abroad, have significant implications for the industry's performance [1]. Accordingly, the U.S. medical device industry devotes considerable resources toward product approval processes, clinical trials, user fees and plant audits/inspections. The U.S. Food and Drug Administration's Center for Devices for Radiological Health (USFDA/CDRH) governs the regulatory oversight of medical devices.

The USFDA maintains three risk categories that determine the type and depth of review necessary for the marketing of medical devices. Process validation is an essential part of medical device manufacturing but doesn't always receive the attention it deserves (and requires). The regulations provide the requirements (FDA QSR 820.75 and ISO 13485 7.5.2), but often manufacturers don't completely understand them and don't fully implement them. The consequences can be audit findings from a Notified Body or Inspectional Observations on an FDA 483.

Validation is in 820.75, and has three components: 820.75(a) relates to the initial validation of a process; 820.75(b) applies to process performance after validation; and 820.75(c) covers process changes or problems.

Process validation is establishing documented evidence that provides a high degree of assurance that a specific process consistently produces a product that meets predetermined specifications and quality characteristics. For this OQ process will be manufacture 1 lot of 59 pieces and for the PQ 3 lots of 59 pieces.

The objective of this validation is to determine that the process works consistently according to plan, for which the system is put to work according to their schedule and all information and relevant data is recorded. The results must demonstrate that the process meets with predetermined specifications.

It should be completed using validated equipment in the specified location and local validated. If the equipment, systems or establishment are modified or changed premises where the process takes place, or the process change, the process must be revalidated after making and approving the qualifications of

systems, equipment and establishment, as appropriate.

Validation Benefits:

- Prevent deviations.
- Optimize the equipment use and the personal in the critical process.
- Make easier the planning and the production control.
- Increase the knowledge about the process and the product.
- Verify the capability of the process.
- Reduce the costs.

The CROSSLINK Spinal System is one such low-profile spinal instrumentation system spine surgeons are using to segmentally stabilize spinal instability and deformity.

In general, crosslinking devices are simple transverse/placed implants that connect the implants (rod) on one side of the spine to the implants (rod) on the other side. The use of crosslinking devices to provide additional stability to posterior spinal instrumentation constructs is universally accepted.

Traditionally, crosslinking devices have been added to the top and bottom ends of rod constructs to increase biomechanical strength (Fig. 1). A drawback to particular crosslinking implants is size - some are bulky. However, low-profile instrumentation is designed to be implanted flatter against a spinal structure - a definite advantage in thinner patients.

In summary, crosslinking devices are extremely important to the ultimate success of reconstructive procedures to treat spinal instability and deformity. The development of the CROSSLINK System is one way spine specialists are working to improve the lives of patients with spinal instability and deformity.

Figure 1
Crosslink System

The Crosslink is comprised of five (5) components, the Break-off Lock, the: Low Profile Break-Off, set Screws (2 Set Screws), the Hook Rod, and the Hook Dish as subcomponents. But just only the Low Profile Break-Off will be the one that will be cover by this validation project.

All (five) components will be affixed together into a single assembly (Fig. 2).

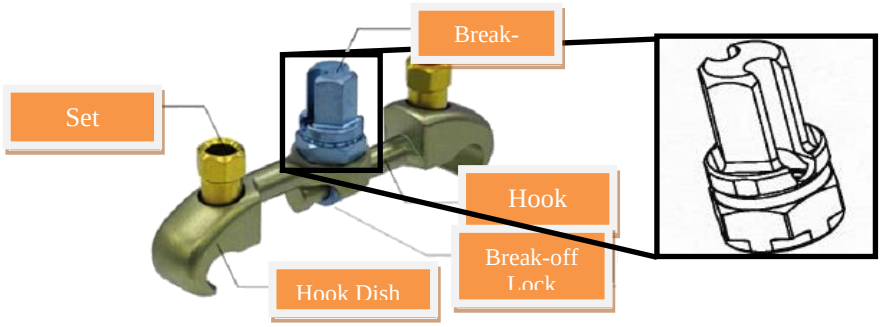

Figure 2
Crosslink Subcomponents Description

METHODOLOGY

After the evaluation of the Essential Design Outputs (EDO) for Crosslink Low Profile Break-Off a total of sixteen (16) were identified but for the purpose of this project just only 4 main characteristics will be take in consideration.

One (1) lot of fifty-nine (59) parts will be manufactured as part of the OQ RUN. Also a total of three (3) lots of fifty-nine (59) parts will be manufactured as part of the PQ RUNS. This all four (4) Runs will be performed at Nominal Settings since the machining process is considered a single set point process determined by the CNC program. This process does not have worst case conditions.

A total of fifty-nine (59) parts for each run will be manufactured for attribute data evaluation per corresponding run. All parts must comply with the attributes specifications. Thirty-five (35) parts will be randomly selected per each run for the variable characteristics evaluation for the qualification activities per corresponding run. Thirty five (35) samples will be satisfactory for this study, as stated in Process Characterization Report previously performed. Thirty (30) samples used in characterization study were sufficient to demonstrate 95%/95% confidence level for all tolerance interval specifications.

The acceptance criteria used for the OQ Run will be to calculate the Tolerance Interval based on required Confidence/Reliability level [2]. If the calculated Tolerance Interval (Upper Tolerance Level UTL or Lower Tolerance Level LTL, based on specification/acceptance criteria) meets specification/acceptance criteria, the runs are deemed to have met predetermined requirements for OQ Run.

The acceptance criteria used for the OQPQ Run:

- Refer to Flow Chart 1 for the Data Analysis requirements of data generated during OQ Run. Document associated data and results in Operational Qualification Run (OQ) Run/Performance Qualification (PQ).
- Refer to Flow Chart 2 for the Data Analysis requirements of data generated during PQ. Document associated data and results in Operational Qualification Run
- (OQ Run/Performance Qualification (PQ).
- Analysis of Variable Data for PQ Only: Perform Analysis of Variance (ANOVA) of the PQ runs. If the resulting ‘p values’ are 0.05 or greater, the PQ runs have demonstrated consistency of the mean and variance. If either ‘p value’ is below 0.05, this indicates that there is a consistency Signal so consistency of the mean and variance has not yet been demonstrated.
- In the event of a consistency Signal Refer to Flow Chart 3 to investigate the signal and determine if the consistency signal observed has a practical significance.

Once the capabilities are done, then the process will be ready to calculate the Sampling plan for each of the characteristics that will exanimated under this validation process.

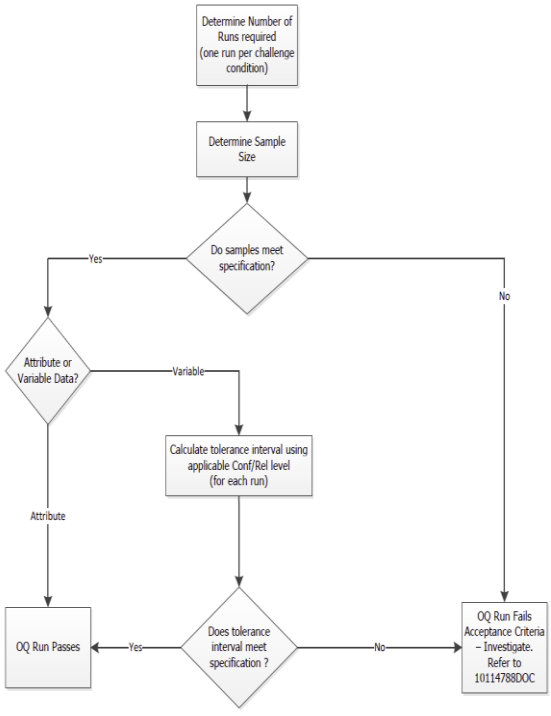

Figure 3
OQ Run – Data Analysis Flow Chart

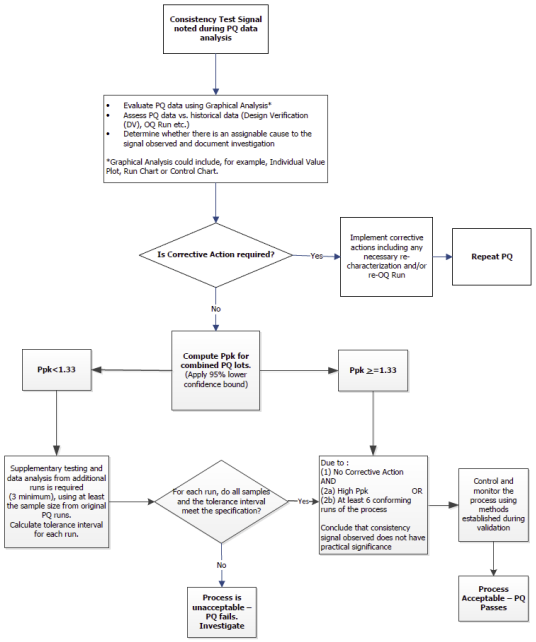

Figure 4
PQ Consistency Signal Flow Chart

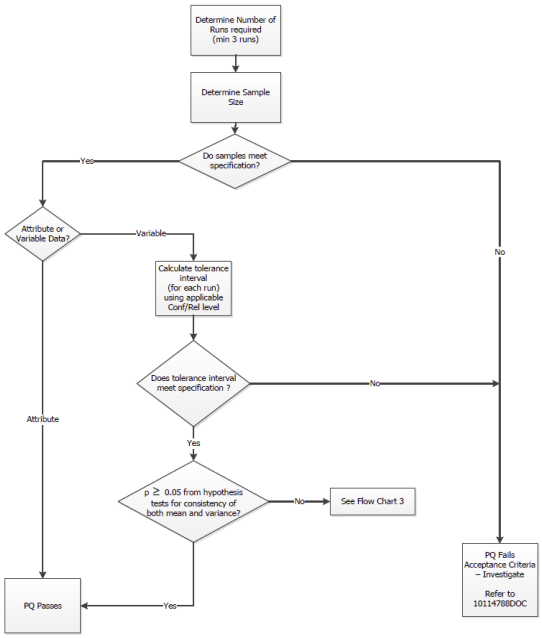

Figure 5
PQ – Data Analysis Flow Chart

OQ EXECUTION

The OQ protocol tests the process produces a consistent product that meet with the design specs. For processes with multiple inputs of varying quality, the OQ can test how the variables of inputs and quality can affect the final product.

Table 1
OQ Run Results

Process Output	Acceptance Criteria	Result	Pass / Fail
¼ -40 UNS-2B Thread	Pass / Fail	All parts met the acceptance criteria	☒ Pass ☐ Fail
12.5 +/- 0.25 Overall length	Tolerance Interval (LSL: 12.25mm / USL: 12.75mm)	Tolerance Interval Results (Lower: 12.441mm / Upper: 12.459mm)	☒ Pass ☐ Fail
2.4 +/-0.2 Thread depth	Tolerance Interval (LSL: 2.2mm / USL: 2.6mm)	Tolerance Interval Results (Lower: 2.389mm / Upper: 2.408mm)	☒ Pass ☐ Fail
9.1 - 11.6 Nm Break-Off Torque	Tolerance Interval (LSL: 9.1Nm / USL: 11.6Nm)	Tolerance Interval Results (LCL: 9.917Nm / UCL: 10.989Nm)	☒ Pass ☐ Fail

The acceptance criteria of this OQ run was to calculate the tolerance intervals of each characteristic, these results must be inside the dimension specification to ensure that with the 95 confidence of level this population will fall between the tolerance interval results. Based on the results, all the characteristic analyzed on this exercise meet the acceptance criteria. This OQ run could be consider passed and good to proceed with the PQ runs.

PQ EXECUTION

The performance qualification protocol (PQ) examines the capabilities of the current process in producing a safe, high-quality product under simulated conditions. The PQ can act as a "stress test" for a product in a controlled environment. The PQ tests assess the final product's adherence to the expectations for its use established throughout the process, as well as the capabilities of the process to deliver the same product quality on a consistent basis.

Table 2
PQ Run Results

Process Output	Acceptance Criteria	Result	Pass / Fail
¼ -40 UNS-2B Thread	Pass / Fail	All parts met the acceptance criteria	☒ Pass ☐ Fail
12.5 +/- 0.25 Overal length	Tolerance Interval (LSL: 12.25mm / USL: 12.75mm)	Run 1 (Lower: 12.441mm / Upper: 12.459mm)	☒ Pass ☐ Fail
		Run 2 (Lower: 12.445mm / Upper: 12.462mm)	
		Run 3 (Lower: 12.432mm / Upper: 12.467mm)	
	ANOVA P value > 0.05	.002	☐ Pass ☒ Fail
	Capability Analysis LB Ppk > 1.33	11.40	☒ Pass ☐ Fail
2.4 +/-0.2 Thread depth	Tolerance Interval (LSL: 2.2mm / USL: 2.6mm)	Run 1 (Lower: 2.389mm / Upper: 2.408mm)	☒ Pass ☐ Fail
		Run 2 (Lower: 2.390mm / Upper: 2.405mm)	
		Run 3 (Lower: 2.391mm / Upper: 2.406mm)	
	ANOVA P value > 0.05	.312	☒ Pass ☐ Fail
	Capability Analysis LB Ppk > 1.33	17.73	☒ Pass ☐ Fail
9.1 - 11.6 Nm Break-Off Torque	Tolerance Interval (LSL: 9.1Nm / USL: 11.6Nm)	Run 1 (LCL: 9.917Nm / UCL: 10.989Nm)	☒ Pass ☐ Fail
		Run 2 (LCL: 10.538Nm / UCL: 11.078Nm)	
		Run 3 (LCL: 9.195Nm / UCL: 11.292Nm)	
	ANOVA P value > 0.05	.000	☐ Pass ☒ Fail
	Capability Analysis LB Ppk > 1.33	0.83	☐ Pass ☒ Fail

The acceptance criteria of this PQ run was to calculate the tolerance intervals of each characteristic, these results must be inside the dimension specification to ensure that with the 95% confidence of level the 95% of this population will fall between the tolerance interval results. Then calculate the Analysis of Variances (ANOVA) to see how the process varies between lots. For this analysis need to meet a P value > 0.05 to demonstrate that the lots means are not significantly different between each other is very un-usual that this ANOVA test pass because the manufacturing process in CNC is very dependable on the machinist offset inputs. The tools gets wear, so the part dimension varies and the machinist need to put some offsets in order to hit the nominal dimension again. In this case just only the "2.4 thread depth" meet this criteria, so following the flow chart 3, a capability analysis will need to be perform in order to see if the process is capable to reproduce the respective characteristics. On this analysis all the characteristics meet the Ppk value > 1.33 except the "Break-Off Torque 9.1 - 11.6 Nm". During the manufacturing process of the third lot, insert T15 (offset T20) broke. Insert was replace but OD offset in T20 was not adjusted as previously run to achieve a Torque value closer to nominal. This caused the process capability of the third lot to affect the overall combined process capability.

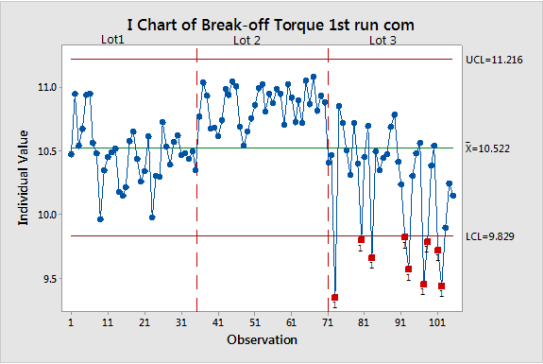

Figure 6
Control Chart Break-off Torque 1st 3 Lots Comparison

As can be seen in the control chart, Torque results were out of statistical control after the replacement of Turning Insert T15. Note that units

are selected randomly and do not represent a run order.

In order to proceed with this process a re-validation of this characteristic was performed, running 3 more lots and need to comply with the tolerance intervals and or the Capability Analysis.

Table 3
PQ Revalidation Run Results

Process Output	Acceptance Criteria	Result	Pass / Fail
9.1 - 11.6 Nm Break-Off Torque	Tolerance Interval (LSL: 9.1Nm / USL: 11.6Nm)	Run 1 (LCL: 10.317Nm / UCL: 11.082Nm)	☒ Pass ☐ Fail
		Run 2 (LCL: 10.415Nm / UCL: 11.040Nm)	
		Run 3 (LCL: 10.563Nm / UCL: 11.083Nm)	
	ANOVA P value > 0.05	.000	☐ Pass ☒ Fail
	Capability Analysis LB Ppk > 1.33	1.81	☒ Pass ☐ Fail

After replacing turning insert in T15, the offset T20 was re-adjusted to run the Break-off Torque at Nominal. Following flowchart 3 after implementing the corrective action, PQ Runs for Torque test were repeated; this time the capability analysis successfully achieved a combined LB Ppk of 1.81.

SAMPLING SIZE

The selected attribute LASP have the same AQL and LTPD levels as variable sampling plans [3]. Attribute LASP require a greater sample size. All inspected units for the lot need to comply with Specification Limits in order to consider the lot acceptable.

- Table 4 lists the AQL & LTPD required to define the lot acceptance sampling plan based on severity and occurrence rating. As the risk increases, the AQL and LPTD values decrease and hence the protection level increases.
- Sampling lot frequency definition will be determined by process owner to maintain sampling uniformity (e.g. per shift, per day, other). The release of the sampling lot will depend on the acceptance or rejection of the sampling plan.
- Table 5 shows variable sampling plans that require a considerably smaller sample size than a comparable attribute sampling plan giving the same protection (i.e. same LTPD).
- If the process qualification data shows that the process is non-normal or the normality cannot be determined, use attribute sampling plans even when variable data is collected.

Table 4
Sampling Plan for Attribute Data

		Occurrence Rating [1]				
		X*≤0.00003%	0.00003%<X≤0.0159%	0.0159%<X≤0.1350%	0.1350%<X≤0.9642%	0.9642%<X
Severity Rating	1	No Inspection Required [2]	No Inspection Required [2]	n = 7 (AQL=1.0 LTPD = 30)	n = 11 (AQL=0.65 LTPD = 20)	n = 15 (AQL=0.4 LTPD = 15)
	2	No Inspection Required [2]	n = 7 (AQL=1.0 LTPD = 30)	n = 11 (AQL=0.65 LTPD = 20)	n = 15 (AQL=0.4 LTPD = 15)	n = 22 (AQL=0.25 LTPD = 10)
	3	n = 11 (AQL=0.65 LTPD = 20)	n = 15 (AQL=0.4 LTPD = 15)	n = 22 (AQL=0.25 LTPD = 10)	100% Inspection Required	100% Inspection Required
	4	n = 15 (AQL=0.4 LTPD = 15)	n = 22 (AQL=0.25 LTPD = 10)	100% Inspection Required	100% Inspection Required	100% Inspection Required
	5	n = 22 (AQL=0.25 LTPD = 10)	n = 45 [3] (AQL=0.15 LTPD = 5)	100% Inspection Required	100% Inspection Required	100% Inspection Required

Table 5

Sampling Plan for Variable Data

Severity Rating	Occurrence Rating [1]				
	Ppk ≥ 1.67	1.67>Ppk≥1.20	1.20>Ppk≥1.00	1.00>Ppk≥0.78	0.78>Ppk
1	No Inspection Required [2]	No Inspection Required [2]	n=5; p(k)=9.45% (AQL = 1.0%, LTPD = 30)	n=8; p(k)=5.93% (AQL = 0.65%, LTPD = 20)	n=9; p(k)=4.06% (AQL = 0.4%, LTPD = 15)
2	No Inspection Required [2]	n=5; p(k)=9.45% (AQL = 1.0%, LTPD = 30)	n=8; p(k)=5.93% (AQL = 0.65%, LTPD = 20)	n=9; p(k)=4.06% (AQL = 0.4%, LTPD = 15)	n=11; p(k)=2.56% (AQL = 0.25%, LTPD = 10)
3	n=8; p(k)=5.93% (AQL = 0.65%, LTPD = 20)	n=9; p(k)=4.06% (AQL = 0.4%, LTPD = 15)	n=11; p(k)=2.56% (AQL = 0.25%, LTPD = 10)	100 % Inspection Required	100 % Inspection Required
4	n=9; p(k)=4.06% (AQL = 0.4%, LTPD = 15)	n=11; p(k)=2.56% (AQL = 0.25%, LTPD = 10)	100 % Inspection Required	100 % Inspection Required	100 % Inspection Required
5	n=11; p(k)=2.56% (AQL = 0.25%, LTPD = 10)	n=17;p(k)=1.31% [3] AQL = 0.15% LTPD = 5)	100 % Inspection Required	100 % Inspection Required	100 % Inspection Required

Table 6

Sampling Size

Control Characteristic	Specification	FMEA Severity	Data Type	Ppk or % Defective	Inspection Level Requirement	Sample Size
1/4-40 UNS-2B Thread Specification	Pass or Fail Pass	4	☒ Attribute ☐ Variable	0 %	AQL= N/A LTPD= N/A	15
12.5 +/- 0.25 Overall length	☒ LSL=12.25 ☒ USL=12.75	3	☐ Attribute ☒ Variable	12.87	AQL= 65 LTPD= 20	8(1)
2.4 +/-0.2 Thread depth	☒ LSL= 2.2 ☒ USL= 2.6	4	☐ Attribute ☒ Variable	20.01	AQL= 4 LTPD= 15	9(1)
9.1 - 11.6 Nm Break-Off Torque	☒ LSL= 9.1 ☒ USL= 11.6	4	☐ Attribute ☒ Variable	2.04	AQL= 4 LTPD= 15	9(1)

For the attribute characteristic of the "Thread Specification" the defective % was "0" and the severity is 4, per Table 4 the Sampling Size is 15 parts per lot need to be measured. For all the variable characteristics the Ppk value were over 2.0 and the higher severity was 4 giving as a result a Sampling Size of 9 parts per lots per Table 5. Therefore all dimensions will adopt the worst case sample size that in this case is 15 units per lot.

CONTROL LIMITS

Control Limits will be used to monitor manufacturing processes. Process monitoring does not replace the product inspections that are currently being performed per applicable product and is not intended to be used to make disposition decisions for individual products, work order, lots, etc. The main objective is to evaluate processes to detect if possible, the occurrence of assignable causes or process shifts so that investigation of the process and corrective action may be undertaken before nonconforming units are manufactured.

Table 7

Control Limits Table

Test Name	Control Limit		Specification Limit	
	LCL	UCL	LSL	USL
12.5 +/- 0.25 Overall length	12.43	12.48	12.25	12.75
2.4 +/-0.2 Thread depth	2.38	2.42	2.2	2.6
9.1 - 11.6 Nm Break-Off Torque	10.02	11.48	9.1	11.6

Statistical Process Control Limits for Low Profile Break-Off was being established based on this qualification results. All characteristics that demonstrated a process capability greater than 2, control limits were set as threshold limits at ±6σ. These limits will serve as adjustment triggers for the operator to adjust tool offsets for wear.

CONCLUSIONS

Crosslink Low Profile Break-Off machining processes are a single set point processes determined by the CNC program and the round stock of raw material. For this reason, the machining process has no worst case conditions to challenge. According to 104788DOC Process

Validation section 5 states [4]: “When no challenge conditions apply, then the process must be qualified using normal operating settings and/or conditions”. Therefore, Operational Qualification run represents and satisfies the PQ first run requirements.

Based on the severity and capability of the control characteristic(s), lot acceptance will be conducted using the sampling plan(s) determined on Table 6.

The Statistical Process Control Limits for Crosslink Low Profile Break-Off documented in Control Limits Table 7 are considered adequate to monitor the process performance and adjust tool wear offset accordingly to maintain the process under control.

The machining process was found adequate to produce Crosslink Low Profile Break-Off units that consistently meet all predetermined requirements at anticipated challenged conditions established in the execution plan, and are considered qualified.

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[3] Medtronic, Sampling Plan Guidelines, MPR-DOC-TMP-008418, Revision 3.

[4] Medtronic, Process Validation, 104788DOC.