Characterization and Extrusion Qualification Process of Introducers/Dilators at Edwards Lifesciences Puerto Rico

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Abstract *— Edwards Lifesciences is experiencing a high demand for Introducers/Dilators. The company decided to produce the Introducers/Dilators single lumen catheters shafts tubing in Añasco, Puerto Rico site. To implement this new production, a qualification process needed to be conducted, involving characterization study to demonstrate equivalency of the material used for component, as well as the qualification of an extrusion process for the catheter's shafts tubing at Puerto Rico. After several iterations, the study of the material demonstrated the equivalence for its use. Also, as results the new extrusion process was achieved to sustain demand.*

Key Terms *— Introducers/Dilators, sheath, FTIR, 4-point bending, Surface Roughness, Dimension, Concentricity, OQ, PQ, Validations*

INTRODUCTION

Edwards Lifesciences is a global company focused on medical innovations centered on structural heart disease, as well as critical care and surgical monitoring. The company is currently experiencing a high demand for products called Introducers/Dilators. The company decided to expand the component's production. As part of this, a component of the Introducers/Dilators, the single lumen catheters shafts tubing which was previously bought from a third party supplier, was now going to be produced in Edward's site in Añasco, Puerto Rico. This new solution will help not only to produce more units to meet demand, but also to avoid buying the component from the external suppliers.

The component is single lumen shaft tubing designed to be used to access blood vessels for the insertion of vascular catheters. The sheath Introducer set comes with a Hydrophilic coating designed for ease used of insertion, and for low profile access in cardiac surgery interventions. The main purpose of is design is to allow space to replace a diseased aortic valve with an artificial valve in the heart.

The Introducer/Dilator acts to stretch the opening in the skin and blood vessel allowing the insertion of the sheath, then is removed, leaving only the sheath inserted, providing a port through to insert the catheter. They are made from a specific resin material that is composed of LDPE DOW 722 (59%), HDPE DOW 8907 (20%), BaSO 4 (20%) and TiO 2 (1%). This shaft tubing come in different French sizes, and they are identified in the hub located at the proximal area for easy identification.

The main objective of this project is to present the strategy of design, development and delivery of one of the main components of the sheath Introducer set, at the same time qualified the extrusion manufacturing process to produce the Introducers/Dilators single lumen catheters shafts tubing in a clean room at the Puerto Rico facilities.

METHODOLOGY

The methodology followed for this Validation process was to perform a characterization study to demonstrate the equivalency of a material already qualified by an external supplier. The feasibility study was conducted with objective evidence and summarized all results of consistency and comparation in the material that was tested, and the final achieve results were documented in a feasibility report. After the completion of the report, the material was challenged in the extrusion process in the extrusion machine at the window operation limit settings for critical parameters to meet pre-

determined requirements per drawings critical dimension and following ISO standards regulations. The results were satisfactory, and the extrusion parameters were also documented OQ/PQ report.

Qualification of the Materials

The focus of the qualification for the material was to perform an analysis of biocompatibility. These tests were necessary for medical devices to meet and comply ISO 10993. Biological evaluation of medical devices recognized by most major national regulatory bodies including the FDA and CE mark as the standard for selecting the biological tests necessary for assessing the safety of a medical device.

To determine which tests, need to be performed and how the medical device is intended to be used, a validation review board is conducted with all the departments. After determining the tests to be performed per ISO 10993-1, a list of the tests was performed based on the area of contact between the medical device and the patient and its duration of contact.

In this case, the biological effect were tested using specific procedures. The medical devices that come in many forms and the organ that comes into contact with it will differ and it is the manufacturer's responsibility to select appropriate tests. ISO 10993 and its subparts contain procedures for testing, but during this assessment it was needed to look beyond those if they are not applicable. The applicable tests procedures required testing which typically involves extracting any leachable substances from the medical device and using them for dosing followed by checking on its effect on the animal, cells, or other agents. Although this standard provides a recommendation on the type of tests to be performed, additional tests may still be warranted depending on the risk analysis, especially for higher risk medical devices [1].

Qualification of the Extrusion Process

The process verification and process validation are two important and commonly misunderstood activities in the development of medical devices. These two activities were required activities for medical the device manufacturer to obtain regulatory clearance to sell their device. Currently, process verification and process validation are not required for medical devices where regulatory clearance is not required, such as point-of-care printing at a hospital.

The 21CFR820 and ISO13485 contain the requirements for design verification and design validation, as well as for process verification and process validation. Design verification and design validation are separate activities from process verification and process validation. Is important to understand the link between design verification/ validation and process verification/validation activities. In virtually all medical devices, there are certain features or characteristics of the device that are important for the device to function properly.

To demonstrate that the manufactured medical device meets the design specifications, the CTQs were challenged to meet the specification requirements. There were two ways to do this, process verification and process validation.

A typical process validation comprises four main elements [2]:

- Installation Qualification (IQ): Simply stated, the IQ is a formal activity to demonstrate that all manufacturing equipment used to produce the medical device has been installed correctly and operates per the manufacturer's specifications. Prior to installing the equipment, an IQ protocol is written to describe the equipment to be installed, the method of installation, and acceptance criteria used to demonstrate that the installation was successful.
- Process Characterization: Once IQ is complete, the next step is to conduct Process Characterization. The purpose of Process Characterization is to understand how the process inputs (X's) affect the process outputs (Y's). Using the process inputs (X's) in the flowchart described in the previous section, a series of experiments is conducted to determine which process inputs affect the process output (Y's), and the allowable limits that produce an

acceptable output. The results of these experiments will be used to establish a processing window for the Operation Qualification (OQ).

- Operation Qualification (OQ): The purpose of OQ is to prove that parts made to the limits of the processing window will meet the design requirements. The first step is to develop the production processing window based on results from the Process Characterization step. The next step is to write an OQ protocol that describes the parts to be tested, the processing window extremes to be challenged, the number of parts to be produced at each processing window extreme, the test method used to evaluate the parts, and the acceptance criteria.
- Performance Qualification (PQ): The PQ demonstrates that the manufacturing process can produce a consistent result using the nominal process setting every time the process is run. The idea is to demonstrate that the process can produce the same result consistently when considering the various sources of common-cause variation, such as manufacturing shut-downs for maintenance, changeovers from one job to the next, raw material lot changes, etc. The first step is to establish the nominal processing settings. Typically, these settings are midway between the extremes established in OQ. The next step is to write a protocol that describes the parts to be tested, the nominal processing window, the number of simulated production runs, the number of parts to be produced per run, the test method used to evaluate the parts, and the pass/fail criteria.

Material Qualification Strategy Focus

The focus of this project stage was to demonstrate the equivalency of the resin material used to produce the Introducers/Dilators single lumen catheters shafts tubing, conduct a feasibility study to summaries the objective evidence, document in a report as baseline the comparison that will sustain the results and recommended operational parameters to comply and demonstrate capability for extrusion process. The material Characterization study tests to be conducted are mentioned in following Figure 1.

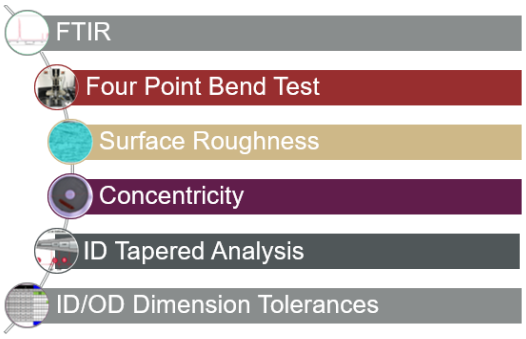

Figure 1
Characterization Study Tests

A feasibility study was conducted, summarizing all the objective evidence of each test, and documented in a Summary Report. The FTIR test is an infrared scan test technique used to identify by light the chemical properties of the material [3]. The second one was the Four Point Bend test, used to measure the force required to bend a material [4]. Another test was the Surface Roughness test used to indicate the level of surface finish of the component [5]. After that, the concentricity test was conducted performing a cross-section of the shaft tube, compare between wall tubing thickness minor wall and maximum wall, to calculate the actual level of concentricity [6]. At the same time, the ID Tapered analysis was performed by cutting the shaft tubing to different lengths in the formed tip area and inspect the inside diameter. At the final test, the ID/OD Dimension Tolerances was measure the to verified that results are within the limits specification as per drawing requirements.

After the completion verification of the dimension analysis, the critical settings operational parameters must be established. For choosing the critical settings operational parameters, and the range selected for challenging the windows limits. The range selected for challenging the window limit were established based on the calibration of the instrument's resolution. In Table 1 are the recommended process parameters to be challenged

along with the range defined for the critical worst-case scenario.

Table 1
Recommended operational extrusion process parameters

PROCESS PARAMETER	Process Range:	Run (Low)	Run (High)
Barrel Zone #1 (°F)	365-370	360	375
Barrel Zone #2 (°F)	365-370	360	375
Barrel Zone #3 (°F)	375-380	370	385
Hd/Clmp Zone #4 (°F)	375-380	370	385
Die Zone #1 (°F)	375-380	370	385
Die Zone #2 (°F)	365-370	360	375
Line Speed (ft/m in)	31.5 – 47.5	30	50

Extrusion Qualification Strategy Focus

This stage was focused on validating the extrusion process, required an Operational Qualification (OQ) extrusion process challenge, at the extrusion machine using operating window limit settings range, under worst case conditions stablished in the baseline report and provide objective evidence that the process produces acceptable product.

After the completion of the OQ qualification, the last phase of the validation process required to conduct a Performance Qualification (PQ) extrusion process, running an operational production process at normal operating paraments and provide objective evidence that the process produces acceptable product under normal operating conditions.

After completion, as defined in the qualification protocol, a specific sample size of the Introducers and Dilators components will be inspected in all its critical dimensions as per drawing acceptance criteria. All the critical dimensions must comply including the visual inspection. In the interim the fill production of samples will be retained until approval of validation report before establishing the disposition of the material.

RESULTS

The tests results obtained in the Material Characterization Study demonstrate the equivalency, and the material challenges at the window operation process limits of the machine settings met the pre-determined requirements.

Material Qualification Results

- FTIR: The resin material and the data points comparison between sample and reference spectra. Based on Figure 2, the results the spectral matches by 99.72%, this is considered similar actual resin versus the actual shaft tube.

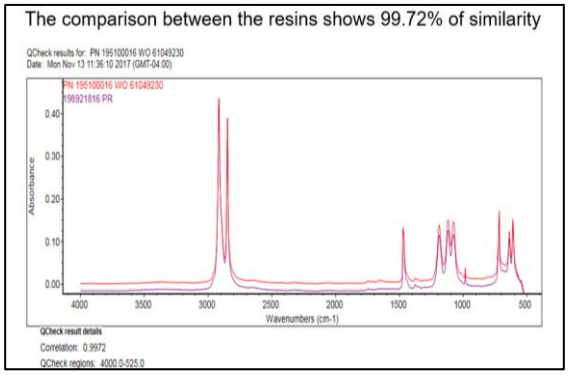

Figure 2
FTIR results

- Four Point Bend Test: The currently external supplier components for the manufacturing of the Introducer /Dilator and the extruded tubing produce in the Extrusion Room 1. Based on Figure 3, the results show than current shaft tube product is between the results obtained when challenging de validated parameters at low and high, therefore, the new extruded shaft tube will not represent a risk to the patient.

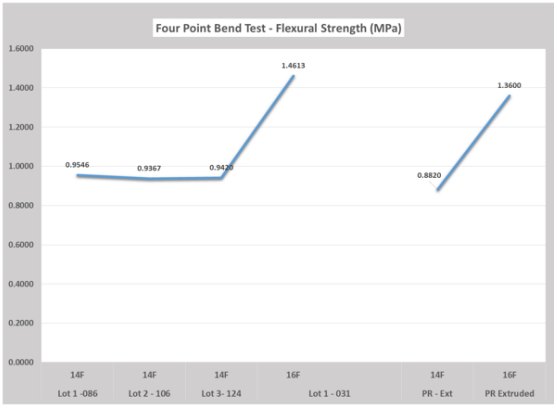

Figure 3
FTIR results

- Surface Roughness: Based on the results of Table 2, it shows that the extruded shafts are

considered more rough than current shaft. Since the parts past through a coating process with a hydrophilic solution, this should help the part to mitigate the lack of solution and help in the bonding in the tube surface, therefore new extruded shaft compares satisfactory to current.

Table 2
Surface Roughness result

22F current	22F Low	22F High
0.5177	0.3644	0.3693

- Concentrcity: After inspected the dimension the concentricity was calculated for the shaft tubing per diameters. As the inside became narrower, the inside diameter became less centered. The bore began to become off-center at approximately 2.00" from the tip. Base on the circular symmetry it was established to set a tolerance for OD and ID.
- ID/OD Dimension Tolerance: As results in Table 3, the samples from the extruded tubing show to met the product specification limits (LSL and USL) per drawing.

Table 3
Dimension Results

	Introducer 14F		Introducer 16F		Introducer 18F		Introducer 20F	
No.	OD	ID	OD	ID	OD	ID	OD	ID
1	0.064	0.037	0.065	0.037	0.066	0.039	0.064	0.040
2	0.063	0.037	0.065	0.038	0.066	0.039	0.062	0.040
3	0.065	0.037	0.065	0.039	0.065	0.037	0.065	0.039
4	0.065	0.038	0.065	0.039	0.066	0.038	0.065	0.040
5	0.065	0.037	0.063	0.037	0.065	0.037	0.065	0.039
	Dilator 22F		Dilator 16F		Dilator 18F		Dilator 20F	
No.	OD	ID	OD	ID	OD	ID	OD	ID
1	0.062	0.040	0.064	0.039	0.067	0.037	0.064	0.038
2	0.066	0.039	0.065	0.039	0.065	0.038	0.066	0.039
3	0.065	0.039	0.065	0.039	0.065	0.039	0.065	0.039
4	0.067	0.040	0.064	0.039	0.066	0.039	0.064	0.039
5	0.065	0.039	0.065	0.037	0.065	0.037	0.065	0.039

OD Spec.	0.065±.005)
ID Spec.	0.039±.002)

Extrusion Qualification Results

To support the build plan for OQ an Extrusion process was be conducted at the window limit pre-stablished. As results in Table 4, the OD was measured, and it was successfully produced within the parameter window limits for extrusion process.

As continued build plant for PQ, the Extrusion process also conducted at the nominal settings to demonstrates that the manufacturing process can produce a consistent for extrusion process. As show in Table 5 the results were successfully satisfactory.

Table 4
OQ Dimension Results

Test	63812295 (18F) Low				Result
	Mean	STDEV	LTL	UTL	
OD	0.063	0.001	0.062	0.064	Pass
ID	0.039	0.001	0.038	0.040	Pass
	63812297 (18F) High				
	Mean	STDEV	LTL	UTL	
OD	0.062	0.000	0.062	0.063	Pass
ID	0.038	0.000	0.038	0.039	Pass
	63812299 (20F) Low				
	Mean	STDEV	LTL	UTL	
OD	0.063	0.001	0.062	0.064	Pass
ID	0.039	0.001	0.038	0.040	Pass
	63812298 (20F) High				
	Mean	STDEV	LTL	UTL	
OD	0.063	0.001	0.062	0.064	Pass
ID	0.040	0.002	0.038	0.041	Pass

Table 5
PQ Dimension Results

Test	63813717 (18F) Nominal				Result
	Mean	STDEV	LTL	UTL	
OD	0.063	0.001	0.062	0.064	Pass
ID	0.039	0.000	0.038	0.039	Pass
	63813718 (20F) Nominal				
	Mean	STDEV	LTL	UTL	
OD	0.064	0.000	0.063	0.065	Pass
ID	0.039	0.000	0.039	0.040	Pass

CONCLUSIONS

The objective of this paper was achieved by presenting that the extrusion runs do not show any material degradation and Qualification of the manufacturing process for the Introducers/Dilators was achieved with no limitation and following the regulatory GMP, GxP's guidelines and regulations, and standard operating procedures for qualification process and sustain demand for next year. After the completion of this qualification is necessary to continued monitoring the process to avoid any implication or influences that might arise in the future.

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