Determination of In-Processing Manufacturing Impact into Elution Rate of Drug Eluting Steroid Collars

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Abstract *— The Food and Drug Administration provides regulations for combination products. The medical device industry needs to comply with these regulations specifically in products containing drug. One of the many regulations drug products need to comply with is the elution rate of the active ingredient. Due to the importance of this performance metric, regulations are becoming stricter regarding tolerances and the compliance with these. Combination products have the complexity of many different manufacturing processes that could have an impact on the elution performance, hence the challenge for medical device manufacturers, to get a good understanding of the different process variables that influence this metric and to establish the appropriate controls. The development work and the costs associated to testing, specification setting and lot release make this particular understanding to be critical for the future and success of the business.*

Key Terms *— Dissolution Rate, Elution Rate Mass Fraction, Potency, Steroid Collar.*

INTRODUCTION

The Center for Drug Evaluation and Research (CDER), a division of the United States (US) Food and Drug Administration (FDA), provides guidance for the performance of combination products related to drug's elution rate. The dexamethasone acetate (DXA) is the active component that is mixed with a silicone elastomer carrier in the form of steroid collars. The elution performance is the result of a multifactorial relation between the collar manufacturing and down-stream processes used for the product manufacturing therefore, the importance of the understanding of the impact of these processes. The focus of this project is the assessment and understanding of the key processes used during the collar manufacturing and the down-stream processes used for the product manufacturing that could have an impact on the elution performance. Individual manufacturing process parameters will be analyzed to determine their relevance to the expected elution performance and assess the potential interactions among processes. For these purposes, a set of individual and combined studies will be performed and results will be evaluated to determine the impact.

RESEARCH OBJECTIVES

This research project intends to determine the impact of the manufacturing processes into the drug collar elution rate. This determination can be used to establish adequate manufacturing process controls and could enable shorter, more accurate new product development cycles. The understanding of the contributing factors would ensure manufacturing consistency, product quality and hence better patient therapy and care.

RESEARCH CONTRIBUTIONS

This project will provide the necessary understanding of the effects of manufacturing key process input variables in the elution performance of drug eluting steroid collars. This task is essential to establish the design space for the process, as well as, the critical quality attributes. This will ensure product quality and compliance and reduced the associated development costs and time.

RESEARCH BACKGROUND

Combination products are defined in 21 CFR 3.2(e). The term combination product includes:

- A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
- A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose;
- Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect [1].

Based on this definition, the combination product to be investigated during this project is considered to be of the nature of the description "a product comprised of two or more regulated components, i.e., drug/device…" (DXA collar/implantable lead). Steroid collars play an important role in the electrical performance of the product by reducing the tissue inflammation hence improving electrical conductivity.

The Center for Drug Evaluation and Research (CDER) performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States.

As part of the U.S. Food and Drug Administration (FDA), CDER regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs. This work covers more than just medicines [2]. As seen in Figure 1, steroid collars are produced by the combination of the active component (DXA) and a silicone elastomer carrier.

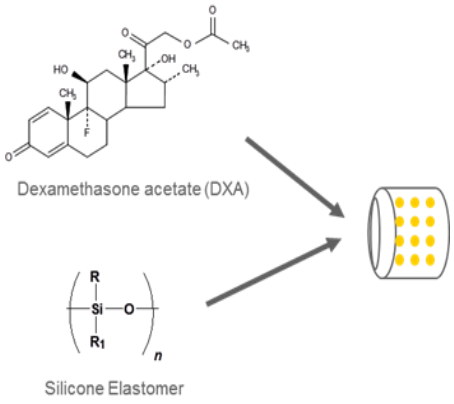


Figure 1
Drug Collar Configuration

The silicone elastomer is made out of two parts and it's mixed in equal proportions with the DXA prior to the molding process. During the molding process the collar's physical dimensions (height, outer diameter, and thickness) are produced. The release mechanism from silicone drug collars is predominantly via diffusion (Figure 2). Its governing equations are derived from Fick's Laws [3], refer to Equations (1) and (2).

$$\frac{\partial M}{\partial t} = PAC \tag{1}$$

Where; M = quantity of material (g), t = time (s), P = permeability coefficient (cm/s), A = area of collar exposed (cm^2), C = concentration (g/cm^3).

$$P = \frac{DK}{h} \tag{2}$$

Where; D = diffusion coefficient (cm^2/s), K = partition coefficient, h = thickness of diffusion layer (cm).

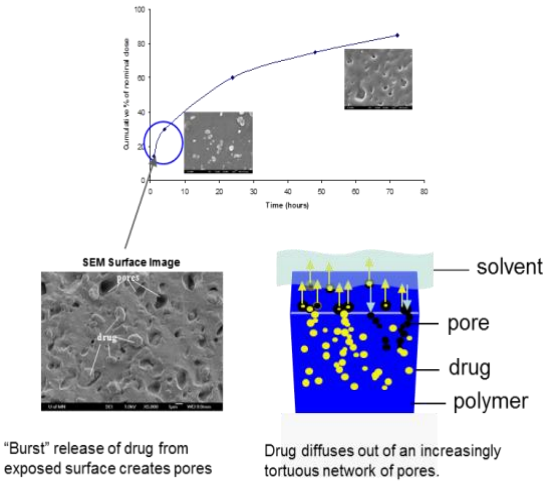


Figure 2
Drug Collar Diffusion Mechanism

Table 1 presents a group of specifications for combination products pertaining to drug performance as established by CDER:

Table 1
Drug Testing and Performance Specifications

Test Description	Specification
Potency (Avg. dose)	Nominal dose +/- 10%
Content Uniformity (USP <905>)	Acceptance value ≤ 15%
Elution	Developed specifically for each test specimen using at least three time points. Results expressed as percentage of nominal dose
Impurities/Degradants (ICH Q3B)	≤ 1.0 % individual impurity, ≤ 2.0 % of total impurities
Identity (HPLC)	Retention time match with USP standard
Identity (FTIR)	Spectrum match with USP standard
Appearance	White, round collar (visually)
Particulates (USP <788>)	10µm: NMT 6,000 25µm: NMT 600
Bacterial Endotoxins	Less than 20 EU/device
Stability Testing (ICH Q1A)	• Potency, Elution, Impurities, etc. • For 2yr shelf life need 12mo data • Data included with submission • Includes Sterility testing

Out of these specifications some are measured at a collar level (potency, mass fraction) and others are measured at a final product level (elution). To minimize the costs associated to the final product testing, representative product samples are used that considers all drug contacting materials and processes that could have an impact on this performance. Elution is defined as the cumulative amount of drug released from the drug component and it's measured at three different time intervals. For our application the amount of DXA drug is quantified at T1 = 1hr, T2 = 4hrs, T3 = 24hrs, T4 = 48hrs, T5 = 72hrs and T6 = 96hrs. Figure 3 presents a graphical representation of the expected drug release percentages at the initial and final time points of the test.

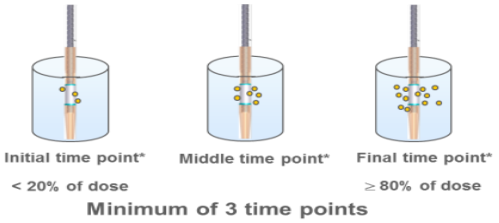


Figure 3
Expected Release at Measured Time Intervals

The data obtained from this testing is used to generate individual values and mean elution plots that are compared against their respective specifications (individuals = 3 time points within ± 20% of tolerance; mean = 3 time points within ± 10% of tolerance). Figure 4 presents an example of an elution profile for the mean of the observed values.

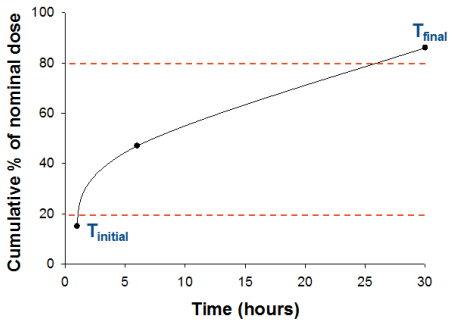


Figure 4
Mean Elution Profile

Since the elution testing is performed at a final product configuration, additional manufacturing processes could have an impact on these results and could be considered as potential sources of variation. These are the basis of investigation of this project. Figure 5 presents a high level process flow for the drug manufacturing, testing and implementation with the final product.

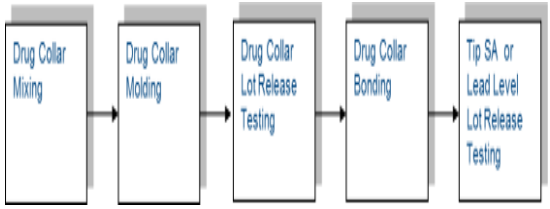


Figure 5
High Level Collar Manufacturing & Testing Process Flow

RESEARCH METHODOLOGY

The methodology to be used in this design project will be the DMAIC Six Sigma Methodology (Define, Measure, Analyze, Implement, and Control). During the Define phase; additional information will be gathered to clarify/support the scope to this project. As well, proper definition of the methods to be used to capture the data will be generated. In the Measure phase; coordinated testing will be executed to generate the required data. Special attention will be placed to the current manufacturing methods and any potential area of opportunity that could be identified as source of variation. During the Analyze phase; a complete analysis of the data that was captured will be generated. Potential solutions will be generated and tested accordingly. If required, will return to previous phases to either organize the work or capture additional data. In the Implement phase; solutions that proved to be effective will be incorporated as part of the normal operation, will ensure proper implementation. With the Control phase; the required monitoring will be set in place to ensure consistent performance and monitoring of any deviation from normal behavior.

RESEARCH RESULTS AND DISCUSSION

This section summarized the findings of this project research following the DMAIC methodology previously explained.

Define Phase

During this phase of the project a cross functional brainstorming session was conducted to consider all potential sources of variation. The areas reviewed encompassed raw materials mechanical properties, surface finish, manufacturing process parameters, manufacturing environmental conditions, design aspects, operator's interactions and test methods used. This exercise helped prioritize focus areas for the investigation. Refer to Figure 6 for a summary diagram**.**

The parameters selected for evaluation where the collar geometry (configurations A, B), tip vs. collar, molding parameters (recipes I, S), tensile strength, percent (%) stretch (0, 25%, 50%) and amount of dispensed adhesive (no adhesive, less, more). Samples were manufactured using these configurations or combinations of these in order to maximize the test articles and opportunities. Elution data was captured and analyzed in each experiment as part of the other project phases.

Measure Phase

Controlled experimentation was conducted to test the different configurations and their interactions were applicable. In the majority of the experiments the measured output variable was the % elution at different time intervals (1hr, 4hrs, 24hrs, 48 hrs.) as required by the regulation. For comparison purposes, the data generated at the 24hr time interval was selected. For the basis of this project two different types of steroid collars were used since the initial elution performance data has indicated different behaviors between the two configurations. Refer to Figure 7 for a graphical representation of these configurations.

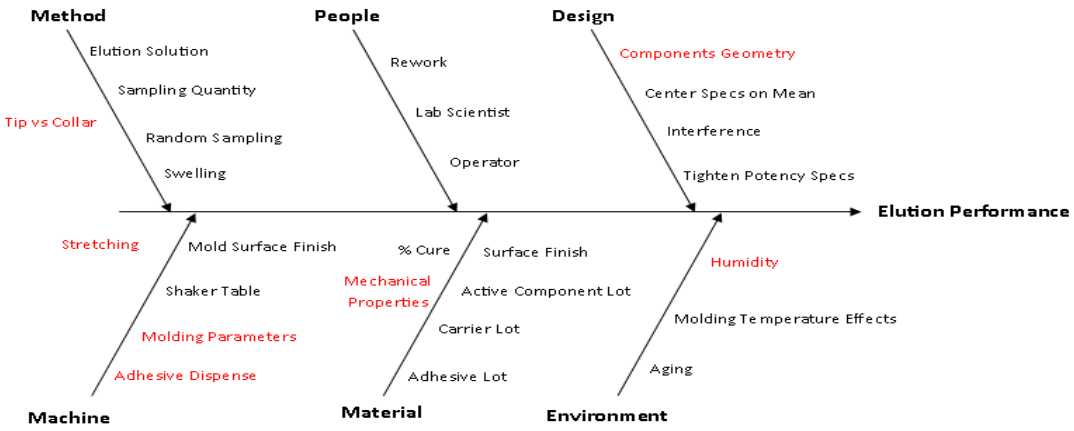


Figure 6
Brainstorming Fishbone Diagram

Figure 7
Collars Configurations A (Left) and B (Right)

Both of these configurations exhibit similar mass fractions (0.31-0.35 mg/mg) but different potencies due to their mass differences (A = 0.91 mg, B = 0.61 mg). When these configurations are tested for elution performance the elution profiles presented in Figure 8 and 9 are obtained.

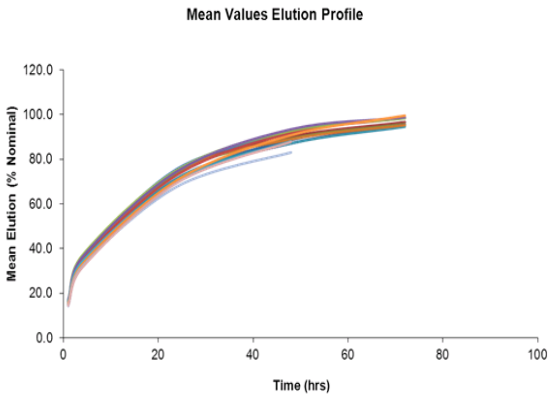


Figure 8
Mean Elution Value for Configuration A

As seen in these graphs the collar configuration A is showing less variation between the samples means than what is seen in the collar configuration B. One of the potential factors causing this difference is the configurations surface areas exposed to the solution. Further explanation of this and other factors will be covered under the Analyze phase of the project.

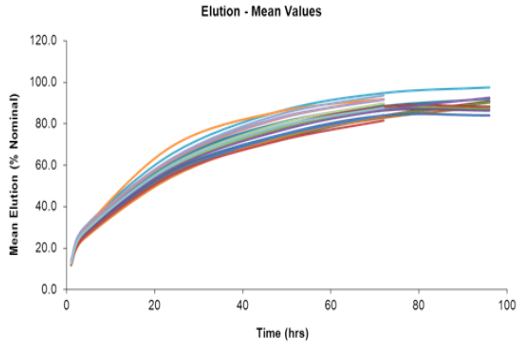


Figure 9
Mean Elution Value for Configuration B

Another factor that was considered during this investigation is the process parameters used as part of the collars molding process. We have investigated to different molding recipes (I, S) that present different approaches to mold the collars. The process approach used with recipe I is to use a lot of pressure and a lot of speed to fill the mold. The fill time used in this recipe is ~ 1.5 sec. This approach tends to produce a denser-less elastic collar because of the use of high packing and

clamping pressure. On the other hand, recipe S uses a lower clamping pressure, variable injection speed (runners fill fast, cavity fills slow ~ 4 sec) and lower packing pressure. The result is a less dense-more flexible collar. As seen in Figure 10 the standard deviations obtained using recipe "S" where lower than those obtained with recipe "I".

Summary Data	1	4	24	48	72
Mean	12.0	22.6	59.0	76.4	85.9
STD DEV	1.244	1.855	3.847	4.321	3.830
% RSD	10.40	8.20	6.52	5.66	4.46

Summary Data	1	4	24	48	72
Mean	13.5	25.3	60.0	77.4	87.6
STD DEV	0.982	1.650	3.270	3.475	3.005
% RSD	7.30	6.53	5.45	4.49	3.43

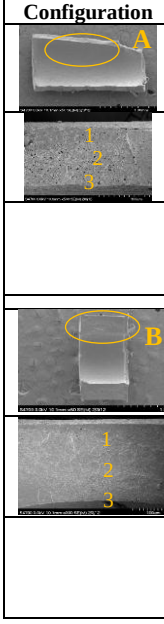
Figure 10
Recipes "I" and "S" Elution Data

One more factor investigated is the percent (%) stretch the collars are exposed to during the assembly process. Collars are loaded into pneumatic pins that are actuated to stretch the collars increasing their inner diameter in order to place the collars on to the product. This stretching process is believed to have an impact on the collar's surface structure affecting their elution rate by the creation of micro cracks on the surface of the collar, exposing more active ingredient to the solution accelerating the elution process. In order to further investigate this theory, both collars configurations (A, B) were stretched to 0%, 25% and 50% increments and scanning electron microscopy (SEM) images were captured. Refer to Table 2 for a summary of the images captured.

As seen in these images, the surface structure of the collars is affected by the stretching during the placement process in the unit. Surface pores are opened exposing more active component into the solution.

In addition to measure the elution performance as a result of these factors, we also intended to understand the effect on the mechanical properties of the collar. For this purpose several samples from the different configurations explained before, were subjected to tensile stress test to investigate if any difference was noticeable after the different treatments. Figure 11 represents collars configuration A, recipes "S" & "I", 50% stretched recipe "S" samples, compared to "OLD" archive collars.

Table 2
Macro and micros images of top cross sections

Configuration	0%	25%	50%
A			
B			

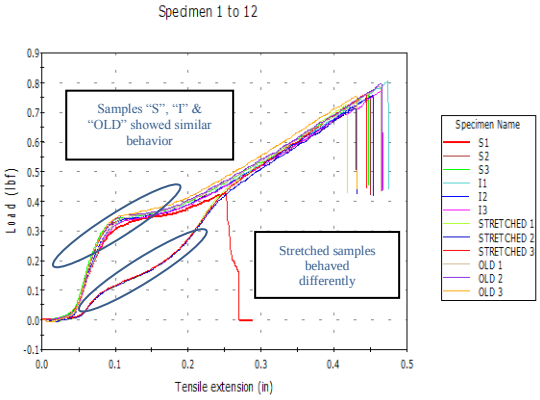


Figure 11
Tensile Strength vs. Deformation; Configuration A

As noted on the graph only stretching the collars had an effect on the tensile strength performance, whereas the rest of the treatments did not make a difference in configuration A. Pre-stretching the collars reduced the force required to achieve a 0.25 in deformation when compared to the rest.

Figure 12 shows the results for similar testing on collar configuration B.

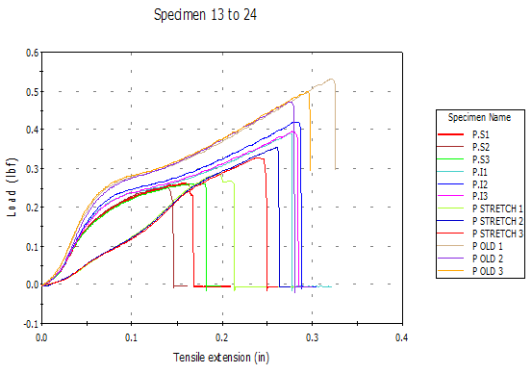


Figure 12
Tensile Strength vs. Deformation; Configuration B

A similar behavior is seen in this configuration, the pre-stretching treatment has an effect on the observed tensile strength. From a collar standpoint, this configuration is showing reduced yield strength when compared to configuration A. This collar cross section is thicker therefore more rigid and less elastic than configuration A. This fact will require additional investigation to further understand the potential effects it could have on surface structure and elution performance.

Two different test methods are used when testing collars and the assembled collars in the test artifact. It has been seen that collars elute faster than the test artifacts due to the exposed surface area. When collars are tested the complete surface area is exposed to the solution therefore one should expect a faster dissolution. But when collars are loaded onto the test artifacts ("tips"), not the entire surface area is exposed due to the components interference and adhesive, therefore a slower dissolution is expected. To prove this, several collars and tips samples were evaluated. Stretched collars were also included as part of this test for comparison purposes. Figure 13 shows the results from this test. As indicated when collars are loaded into the test artifacts the dissolution rate is slower than when tested individually. It can also be seen that stretched collars tend to elute slightly faster than normal collars.

The last factor studied in this investigation is the amount of adhesive applied to attach the collar to the tip. Due to the importance of the exposed surface area to the elution rate it is believed that the amount of applied adhesive plays an important role in reducing the elution variation. For this test, three levels of adhesive were determined to be challenged. "Low Adhesive" (Low MA) is considered to use lower amounts of adhesive than those validated as part of the manufacturing process. "High Adhesive" (High MA) is considered to use an excessive amount of adhesive, greater than those permitted by the validated manufacturing process. The last treatment is "No Adhesive" (No MA) to challenge the extreme condition of not having any adhesive present. Table 3 presents the results of this testing.

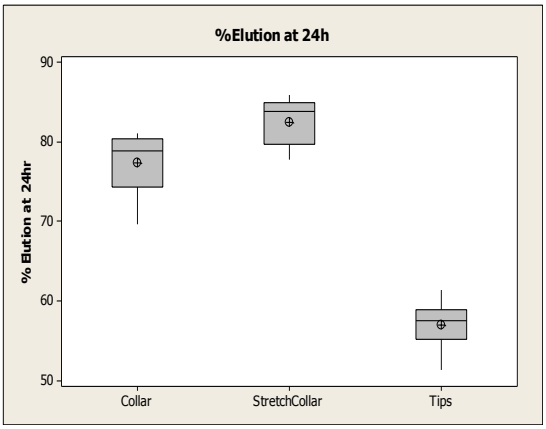


Figure 13
Elution Percent at 24 hr. Collar vs. Tips Comparison

Table 3
Elution Percentages for "Low, High and No MA"

		Percent Dose Eluted				
		0	1	4	24	48
2110000001	Average	0	16.2	33.3	75.5	93.3
Low MA	%RSD	n/a	3.9	2.5	1.9	1.1
2110000011	Average	0	15.8	31.5	74.2	92.1
Low MA	%RSD	n/a	2.8	2.7	1.6	0.4
2110000001	Average	0	14.8	30.3	73.1	93.2
High MA	%RSD	n/a	4.5	5.4	8.8	3.4
2110000011	Average	0	15.3	29.4	73.7	92.6
High MA	%RSD	n/a	3.3	2.5	3.0	0.7
2110000001	Average	0	18.4	36.9	83.5	96.9
No MA	%RSD	n/a	5.0	3.6	2.5	1.3
2110000011	Average	0	17.1	31.7	77.0	93.1
No MA	%RSD	n/a	0.6	2.4	1.1	1.5

Contrary to what was expected, no significant difference was observed between treatments indicating that there might be other factors governing the variance.

Analyze Phase

Through the experiments conducted during this investigation several theories were challenged in order to get a better understanding of the factors governing the variance observed during the steroid collar drug elution test. We learned that collar geometry plays an important part in determining the surface area that will be exposed to the solution one of the factors in Fick's law. Also geometry has a direct indication into the collar's mechanical properties specifically on surface structure. We also learned that the processes used to stretch the collar before placing them into the product could create small cracks in the surface of the collar that could produce additional pathways for the solution to access the active ingredient causing dissolution. By mechanical means these processes could be easily controlled but the impact they have on the collar surface is very random and difficult to control.

We also investigated the effects of the molding process parameters in the dissolution rate. Collars that are produced at higher injection speeds, higher packing pressures and clamping pressures, could produce collars with higher variation and standard deviation. Even when the tensile strength test prove that there is no difference between these collars and those produce at lower injection pressure and speeds, they seem more difficult to control and produce consistently. More malleable and flexible collars produced at lower injection and packing pressures behave more consistently and with less variation.

During the assembly process collars are subjected to stretching in order to be loaded into the product. This stretching process mechanically deforms the collar structure creating additional elution paths. Controlling the stretching process and the molding parameters could produce a successful combination for elution variance reduction. Further understanding of the effects stretching has on the collar properties is recommended. This was the only treatment that showed a difference on the collars yield strength.

Adhesive application surprisingly did not have a significant impact on the elution performance even at its extremes (Excessive MA – No MA). But when compared collars vs. tips, it was noted a significant difference indicating the importance of the test method used. Maybe there is no clear factor that we could point to as the responsible for controlling the elution variation but instead, a combination of factors that when present in the right distribution, causes results to shift from one side to the other and leaving us with no clear understanding of why.

Implement/Control Phases

As part of the implement phase several suggestions come to mind as of what to do moving forward. One should take advantage of the benefits every one of the options we tested during this investigation presented and implement them accordingly. Standardizing collars sizes and geometries to those that have proof to be beneficial. Adhere to process parameters that reduce stress in the parts. This should yield more consistent, controllable and predictable parts that should behave more consistently. Seek for further understanding of the mechanics of the stretching process and its effect on surface finish. As part of the control phase, continue monitoring performance, continue listening to the variables so that we could really understand the one or the perfect combination of the few that drive this metric.

CONCLUSIONS

This research project has provided the opportunity to challenge and test many of the unknowns and theories regarding the impact of drug collar manufacturing and down-stream process into the elution performance. Many of the aspects regarding collar geometry, molding parameters, collar stretching, adhesive amount, lot to lot material variation, within collar lot variation, surface finish, test method, surface cleaning, among others were tested and prove to have no single

impact or significance in determining the elution variation. Not all these results were covered as part of this investigation report but were equally tested. No single item was identified as the lever to use to manage this variation. Clear indications of the importance of process parameters control through the molding recipe, collar stretching control during the assembly process and reduced morphology changes in the collar surface will help improve elution performance and minimize variation. The combination of multiple factors could be the assignable cause for the variation. Further studies should focus on investigating these combinations to successfully identify the real levers to use to control, predict and manage this variation ensuring reduced costs, faster development timelines, better product quality and customer satisfaction.

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