Design Project for Process Improvement of the Manufacturing of Electrode Ring – Monolithic Controlled Released Devices (MCRDs)

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Abstract *— Medtronic Rice Creek Pharmaceutical Operations at Fridley, Minnesota currently build the Electrode Ring, Monolithic Controlled Released Device (MCRD) assembly which is sent to Medtronic Villalba Campus (MVC). At MVC, the Electrode Ring MCRDs go through a various of manufacturing process to untimely build the final product which is a Pacemaker Lead cable.*

Key Terms *— DMAIC, MCRD, DXAC, LBM.*

PROBLEM STATEMENT

Currently Medtronic Rice Creek Pharmaceutical Operations at Fridley mixes 250 grams of Dexamethasone Acetate (DXAC) and Silicone Rubber which is then molded to form 960 units of MCRDs Rings. Only 0.24 grams is used to manufacture the 960 units and the remaining 249.76 grams is scrapped and considered as waste.

Research Description

This project has been outlined to provide a basic overview about the heart physiology, pacemakers, defibrillators or cardiac resynchronization devices. Subsequently, the manufacturing procedure of the assembly containing the drug component of the steroid-eluting lead will be address with the purpose of improving the current process at Medtronic Rice Creek Pharmaceutical Operations at Fridley, Minnesota. The intention of providing an overview of the pacemakers in general before focusing on the manufacturing of a specific assembly is to highlight why it is important to be very robust in the implementation of a process improvement project since the life of patients depend on these devices.

Research Objectives

This objective of this research is to develop an effective, sustainable, and quality driven strategy to improve the manufacturing process of Electrode Ring – Monolithic Controlled Released Devices (MCRDs) with the purpose of reducing cost and maximizing material usage.

Research Contribution

The project developed as part of this research process will be implemented at Medtronic Pharmaceutical Operations at Minnesota, Minneapolis. After implementation of the project Medtronic will be incurring in a yearly cost saving amount of $850,000. In addition, the project will serve as the first phase to transform the manufacturing line for the Electrode Ring MCRD from its normal batch and queue system to a cell operating system (COS).

RESEARCH BACKGROUND

The cardiac muscle is shaped to form four cardiac chambers, the two upper chambers are called an atrium and the other lower two chambers are called ventricle. The flow of blood through the heart is as follows: the right atrium contracts and pumps blood through the tricuspid valve into the right ventricle. The blood then goes through the pulmonary valve into the pulmonary artery, which delivers the blood to the lungs. In the lungs the blood takes on oxygen and releases its carbon dioxide. The oxygenated blood is pumped from the left atrium, through the mitral valve, into the left ventricle. Finally, during contraction of the left ventricle, the oxygen-rich blood is pumped through the aortic valve into the aorta and branching arteries to be delivered to all the organs of the body. The

Figure 1 provides an illustration of blood flow through the heart.

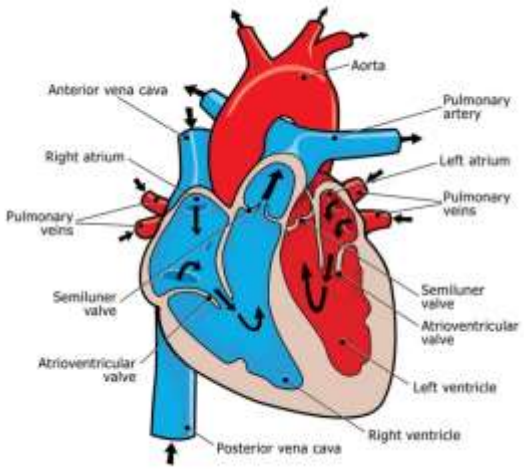

Figure 1
Illustration of Blood Flow through the Heart

Heart Failure (HF) is a condition that reduces the heart's ability to pump blood. It can result from a heart attack, untreated high blood pressure, or abnormality of one of the heart valves. The damage muscle due to heart failure has a less effective pump resulting in the reduced ability to supply oxygen to meet the needs of the body and brain.

The cardiac conducting system (CCS) generates electrical impulses which are rapidly conducted through the heart muscle. The elements of the CCS are the following: the sinoatrial node (SA Node), the atrioventricular node (AV node), the bundle of His, the right and left branches and the Purkinje Fibers. The SA node is responsible for initiating the electrical impulse that causes the heart to beat. This impulse travels throughout the cells of the atria then continues on to the AV Node. The AV node serves as a "gatekeeper" delaying the e electrical impulse before relaying it on to stimulate the ventricles, this slight delay ensures that the r right and left atria have had sufficient time to contact before the ventricles do. The impulse then travels on to the right and left ventricles through the Bundle of His. Finally, the impulse is passed through the muscle cells of the ventricles causing them to contact and forcefully eject the blood contained within. Figure 2 provides a representation of the electrical conducting system of the heart.

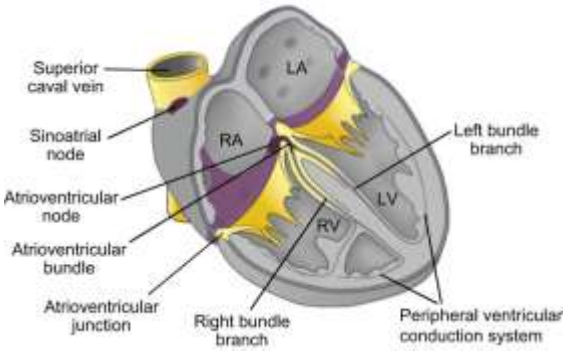

Figure 2
The Electrical Conducting System of the Heart

A pacemaker system consists of two parts: a pulse generator, also known as pacemaker, implantable pulse generator or IPG, and one or two lead(s). Pacemaker system is illustrated in Figure 3.

Figure 3
Pacemaker System Manufactured by Medtronic

The system performs two main functions: diagnosis function to sense intrinsic cardiac activity and the treatment function to emit an electrical I impulse that excites cardiac cells and produces a wave of depolarization in the myocardium. The leads are an important component of a pacemaker system, they are introduced through the vessels of the upper venous system. The leads carry the electrical impulse from the device to the heart and relay information about the heart's natural activity back to the device. An illustration of a lead is presented in Figure 4.

Figure 4
6947M Lead Model Manufactured by Medtronic

The primary purpose of the lead electrode is to act as a long-term interface between the lead and the heart muscle. It is through this interface that the electrical stimulus passes. The other purpose for the electrode is to sense intracardiac signals for the pacemaker to monitor and to ensure proper pacing when necessary. The electrode must contact the heart in a manner that it is as stable and atraumatic to the tissue as possible and produces minimal inflammatory and fibrotic responses. A visual presentation of the lead implanted in the heart is illustrated in Figure 5.

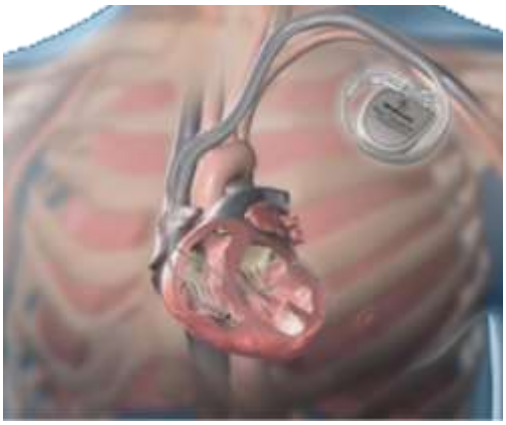

Figure 5
Pacemaker System Manufactured by Medtronic Implanted in the Heart

The electrically conductive materials that are used for the surface material of pacing electrodes are platinum, platinum-iridium alloy and activated carbon.

The information regarding pacemakers and the heart physiology was provided by the Handbook of Leads for Pacing, Defibrillation & Cardiac Resynchronization, First ed., Erick Cuvillier, Medtronic, Villalba, Puerto Rico, 2019. [1]

Manufacturing Process for Electrode Ring MCRDs

The manufacturing process begins with the enhanced tear resistant (ETR) rubber and DXAC being weighted separately and then mixed using a mixing equipment. Four mixes are created per lot of DXAC/Silicone Rubber which are labeled as A-R01, A-R02, B-R01 and B-R02. Afterwards the mixture is loaded into a milling machine to combine child lots A-R01 + AR02 to form A1 and B-R01 + B-R02 to form B2. Subsequently, both Rubbers A1 and B2 are divided into 4 child lots (A1-4) and (B-4) which then are combined as detailed in Figure 6.

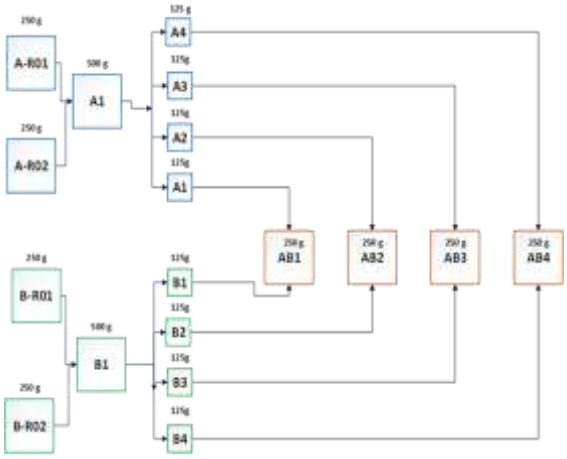

Figure 6
DXAC/Silicone Rubber Mixing and Milling Process Flow

The material is divide to shots of 4-grams and placed in a stainless-steel container. The 16-cavity mold is pushed into the hot transfer press machine (Refer to Figure 7).

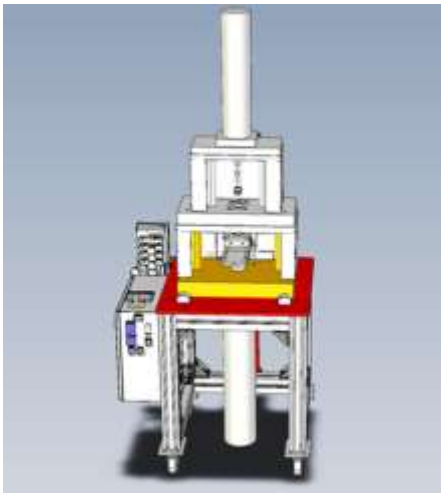

Figure 7
Hot Transfer Press Computer-aided Design (CAD)

Subsequently, a 4-gram shot is placed in the hot transfer press material transfer tube and sensors are used to actuate (lower) the ram and start the press cycle by feeding material into the mold. After hot transfer press completes the cycle time, the mold is taken out and the sprue/excess material is removed from the mold and ram. The MCRDs are then taken out of the mold and inspected to segregate defective parts (Refer to Figure 8).

Figure 8
Molding Process

After the molding process is completed, the rings are inspected for flash, trimmed (if necessary) and then acceptable parts are oven-cured for six (6) hours. After curing, parts are removed from the oven and washed by placing into an amber glass jar filled with sterile water, 200 mL. The jar is placed onto an orbital shaker at 200 rpm for thirty (30) minutes to facilitate the removal foreign material. After shaking, the jar is removed from the orbital shaker and vacuum-filtered through a Nalgene filter jar. Rings are then removed from the filter jar onto a rice paper lined stainless-steel container were the parts are air dried for a minimum of thirty (30) minutes.

After drying, rings are assembled onto electrodes. An assembly fixture spins the electrode while a needle dispenses adhesive into the electrode center channel and the ring is inserted into the electrode channel containing adhesive. After the ring is installed, the assembled electrode rings are 100% inspected for cosmetic and functional defects. Acceptable parts are placed into a-well tray, allowing them to cure at room temperature for an additional 72 hours. Refer to figure 9 for image of Electrode Ring without MCRD assembled and Electrode Ring with MCRD assembled.

Figure 9
Electrode Ring (Left) and Electrode Ring with MCRD (Right)

During final packaging, well trays containing the acceptable parts are covered with a lid and heat-sealed into polyethylene bags. Each polyethylene bag is then packaged into a mylar bag and sealed with a heat sealer. The Electrode Ring MCRD component once manufactured at CRHF-Fridley (upon obtaining conforming lot released results) are shipped to downstream Medtronic facilities for finished goods manufacturing. Attain Ability Straight MRI Surescan Model 4396 is an example of a lead model that uses the Electrode Ring MCRD (Refer to Figure 10).

Figure 10
Attain Ability Straight MRI Surescan Model 4396

METHODOLOGY

The problem-solving methodology used for this project is called DMAIC which stands for Define, Measure, Analyze, Improve and Control.

- Define - To develop a clear project charter based on a real problem that is relevant to the customer, and that will provide significant benefits to the business.
- Measure-To understand and baseline the current performance of the process, through a set of relevant and robust measures.
- Analysis - To find the root causes of the problem and understand their effect on process performance.
- Improvement - To develop, select and implement the best solutions, with controlled risk.
- Control - To ensure the solutions are embedded, the process has robust controls, and the project has clear closure.

The problem-solving methodology was performed using the following book as reference: Issa Bass, Barbara Lawton, Ph.D. “Lean Six Sigma, Using Sigma XL and Minitab”, First Edition (McGraw Hill: New York Chicago San Francisco Lisbon London Madrid Mexico City Milan New Delhi San Juan Seoul Singapore Sydney Toronto [3].

RESULTS AND DISCUSSION

The Define Phase was initiated with the creation of a project charter which is a formal, typically short document that describes your project in its entirety — including what the objectives are, how it will be carried out, and who the stakeholders

are. It is a crucial ingredient in planning the project because it is used throughout the project lifecycle.

Project Name - Design Project for the Manufacturing of Electrode Ring – Monolithic Controlled Released Devices (MCRDs).

Background / Problem Statement - Medtronic Rice Creek (RC) Pharmaceutical Operations at Fridley, Minnesota is the only Medtronic site that manufactures drug components for the medical devices that the company builds. Currently, Medtronic RC for the manufacturing of the Electrode Ring – Monolithic Controlled Released Devices (MCRDs) mixes 250 grams of Dexamethasone Acetate (DXAC) and Silicone Rubber which is then molded to form 960 units of MCRDs Rings per child Lot. Only 0.24 grams is used to manufacture the 960 units and the remaining 249.76 grams is scrapped and considered as waste. In addition, before the units can be shipped out each lot most be sent to the analytical laboratory to be tested as part of compliance requirement 21 CFR Part 4, which is the current Good Manufacturing Practice (cGMP) requirements for Combination Products.

Business Objectives - Reduce material and labor costs, reduce defectives units, reduce units sent to product hold and increment quality/reliability of the Electrode Ring MCRD assemblies manufacture at Medtronic Rice Creek (RC).

The Project Scope & Assumptions were the following:

- In Scope - Electrode Ring MCRD manufacturing operations from the MCRD molding process up to the Electrode Ring MCRD inspections process (Operation #5 to Operation #10 as identified in Figure 6 of this document).
- Out of Scope - The analytical submission to quality audit processes (Operation #11 to Operation #13 as identified in Figure 6 of this document).
- Project Team & Timeline.
- Project Leads- Jordi Martin / Juan Fernandez.
- Project Champion - Michael Lybarger.
- Proposed Team Members - Chris Messerli, Bret Peterson, Katie Bultman, Trey Poole, Pattie Keute.
- Stakeholder – Sarah Ren (Manufacturing Engineering Manager) and Dave Connelly **(**Manufacturing Operations Manager).

The key findings after the investigation performed during the define phase are the following:

- **Waste in Material Utilization:** 0.24 grams is used to manufacture the 960 units and the remaining 249.76 grams is scrapped and considered as waste.
- **Unit Count Discrepancy:** Every single unit is counted and inspected throughout the manufacturing process for Electrode Ring MCRDs. The highest indicator for lot production hold is “Units Miss Counts”.
- **Line Balance:** Child lot quantities distribution could be improved to enhance units’ movements throughout the manufacturing process.
- **Pharmaceutical Testing:** The amount of testing release per lot has a significant cost per year.

The Measure Phase initiated with the creation of a Cause-and-Effect Diagram. The engineering team and the manufacturing team members got together to work as team developing a Fishbone diagram or also known as a cause-and-effect diagram. This helped the team to understand and identify possible contributing factors or causes that might influence the identified problem. A fishbone diagram is a visual way to look at cause and effect. (Refer to Figure 11).

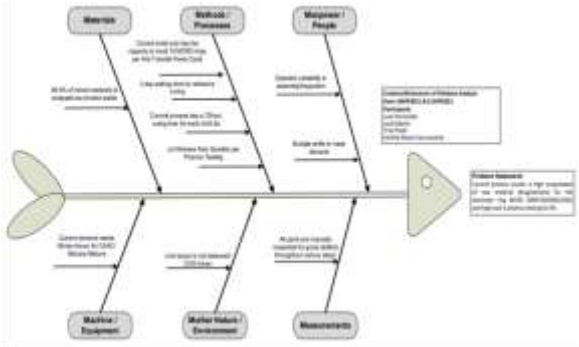

Figure 11
Cause and Effect Diagram

The overall manufacturing process for Electrode Ring MCRDs is detailed in Figure 12.

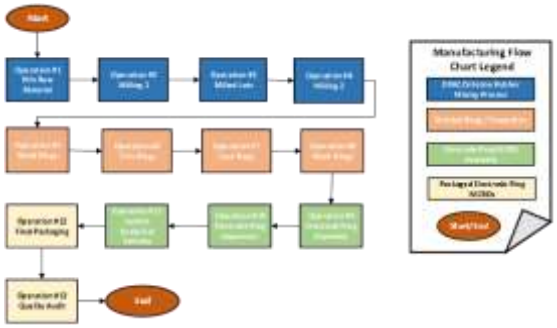

Figure 12
Process flow chart for Electrode-Ring, MCRD

The molding process performance is measured as follows:

- Part yield for Electrode Ring MCRDs: Average of 93% for Fiscal Year 2020 to Fiscal Year 2021.
- Raw material yield at molding:
  - Start: 250 g of material per child lot; 1kg per lot
  - End: ~249 grams of process loss, 0.992 kg per lot
  - Yield: 0.24 grams of parts/249 g starting material = 0.096% raw material yield.
  - Refer to Figure 13 for a linear time graph of the production yield % throughout FY20-FY21.

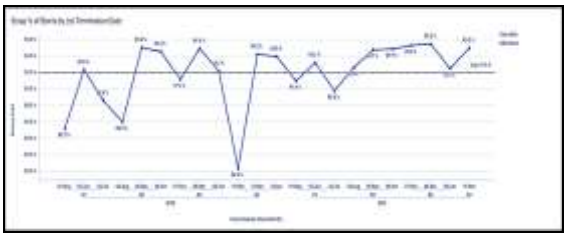

Figure 13
Production Yield % Throughout FY20-FY21

The current process state/costs related to Labor, Burden and Material (LBM)

- LBM in FY21 was $1.5 mil
- 110 lots manufactured
- Approximately 400,000 individual MCRDs manufactured
- Total LBM (cost associated to labor, burden and materials) in FY21: ~$1.5 mil

The Analyze Phase consisted of the creation of Design of Experiment (DoE). The current qualified molding process uses a 16-cavity mold producing 16 ring MCRDs per sprue from approximately 4 grams of DXAC (Dexamethasone Acetate) / Silicone Rubber mixture. The 32-cavity mold has been designed for use on the same manufacturing line, using the same amount of material to increase the completed molded ring MCRD quantity by reducing excess material waste (Refer to Figure 14 for image of both the 16 cavity and 32 cavity mold). The 32-cavity mold was used as part of this DoE to ensure that validated Hot Transfer Press operating parameters for the molding process will produce acceptable ring MCRDs or if the parameters needed to be updated.

Figure 14
16 Cavity Mold (Left) and 32 Cavity Mold (Right)

- Process Inputs: Mixed Material Quantity (Silicone Elastomer and Dexamethasone Acetate Weight), Weighed Material ('Shot') weight, Refrigerator Temperature, 16-cavity mold tool, 32-cavity mold tool, HP Clamp Pressure, HP Transfer Pressure, Ram Time, Clamp Time, Platen Temperature, LP Clamp Pressure and LP Transfer Pressure
- Process Outputs: As part of this process development report, the process yield will be evaluated for the ring MCRDs molded with the 32-cavity mold. Manufacturing yield has a minimum target metric for operations of 90%. The yield metric is used as a control for manufacturing and does not affect form, fit, or function. After the visual inspection, acceptable manufacturing samples were randomly selected and submitted for analytical lot release testing, to demonstrate compliance with acceptance criteria for the pharmaceutical testing. This data is not a direct output of the molding process; however, it was determined that analytical lot release data was the best option to evaluate the effects of the process change on product

function despite no change to the Silicone/DXAC material quantity or mix process. Acceptance Criteria is established using Part 211 -- Current Good Manufacturing Practice for Finished Pharmaceuticals reference [2].

- MCRD Visual Criteria - MCRD is free of visual defects described as foreign material, voids, discoloration, and nicks/cuts.
- Description - MCRD ring made of white to off-white colored polymer is positioned in the center channel of a ring electrode.
- Assay/HPLC - Label Claim: 90% to 100% of Label Claim (%LC)
- Degradation Products - are unwanted chemicals that can develop during the manufacturing, transportation, and storage of drug products and can affect the efficacy of pharmaceutical products.
- Content Uniformity - The requirements for dosage uniformity are met if the acceptance value (AV) of the first 10 dosage units is less than or equal to L1%. If the acceptance value is greater than L1%, test the next 20 units and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1% and no individual content of any dosage unit is less than (1- L2·0.01) M or more than (1+L2·0.**01) M.**
- Identity: UV/PDA - The UV absorption spectra of the test solution and the standard solution exhibit maxima and minima at similar wavelengths.
- Identity: UPLC - The retention time of the dexamethasone acetate peak in the assay sample preparation is within ± 5% of the mean retention time of the dexamethasone acetate peak in the bracketing standard injections.
- Identity: IR - The IR absorption spectrum of the sample exhibits maxima at similar wavelengths as that of corresponding reference standard.
- Elution - The "elution time" of a solute is the time between the start of the separation (the time at which the solute enters the column) and the time at which the solute elutes.
- Challenge Conditions for Hot Transfer Press
- Low Challenge Conditions - Low process parameters at the mold press would potentially lead to the mold cavities being under-filled at the molding step, which could lead to Incomplete Fill scrap or voids in the material identified at downstream processing steps.
    - HP Clamp Pressure: 61 psi
    - HP Transfer Pressure: 35 psi
    - Ram Time: 8 Seconds
    - Clamp Time: 90 Seconds
    - Platen Temperature: 240°F
    - LP Clamp Pressure: 85 psi
    - LP Transfer Pressure: 50 psi
- High Challenge Conditions - High process parameters at the mold press would potentially lead to the mold cavities being over-filled at the molding step, which could lead to flash at downstream processing steps
    - HP Clamp Pressure: 74 psi
    - HP Transfer Pressure: 58 psi
    - Ram Time: 12 Seconds
    - Clamp Time: 110 Seconds
    - Platen Temperature: 260°F
    - LP Clamp Pressure: 95 psi
    - LP Transfer Pressure: 70 psi

Below are presented the results summary which detailed the different outcomes of the experiments.

- Experiment #1: "*Special Work Request (SWR) Report for Electrode Ring MCRD using 32-Cavity Mold"*

The purpose of this experiment was to provide objective evidence that the manufacturing molding process meets predetermined requirements, as per lot release specification "Steroid Lot Release Document for Electrode – Ring, Radiused MCRD", under challenge conditions using the 32-cavity mold design tool instead of the current 16 cavity mold tool. The Special Work Request consisted of 3 builds each performed with different challenge conditions for the pressing procedure.

Build 1 Low Settings: Results Summary

Below in Table 1 is presented the Electrode Ring MCRD Testing Results against the pharmaceutical acceptance criteria. In addition, in

Figure 15 the elution testing results are presented in a Time Graph.

Table 1

Electrode Ring MCRD Testing Results (Low Settings)

Lot Number	R141520RBEDF		
Test Description	**Component**	**Result Value**	**Pass/Fail**
Description	Visual P/F	Pass	Pass
Identity	Percent Diff Sample from Standard	0 %	Pass
	ID UV P/F	Pass	Pass
Content Uniformity / UPLC	Stage 1, Acceptance Value (AV) A	5.7	Pass
Assay / UPLC	Dexamethasone Acetate	97.7 % LC	Pass
Degradation Products	Total Impurities	0.5 %	Pass

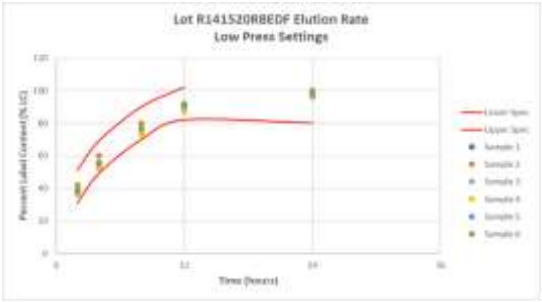

Figure 15

Elution Rate Results Chart

Build 2 Nominal Settings: Results Summary

Below in Table 2 is presented the Electrode Ring MCRD Testing Results against the pharmaceutical acceptance criteria. In addition, in Figure 116 the elution testing results are presented in a Time Graph.

Table 2

Electrode Ring MCRD Testing Results (Nominal Settings)

Lot Number	R141520RBABC		
Test Description	**Component**	**Result Value**	**Pass/Fail**
Description	Visual P/F	Pass	Pass
Identity	Percent Diff Sample from Standard	0 %	Pass
	ID UV P/F	Pass	Pass
Content Uniformity / UPLC	Stage 1, Acceptance Value (AV) A	3.5	Pass
Assay / UPLC	Dexamethasone Acetate	99.3 % LC	Pass
Degradation Products	Total Impurities	0.4 %	Pass

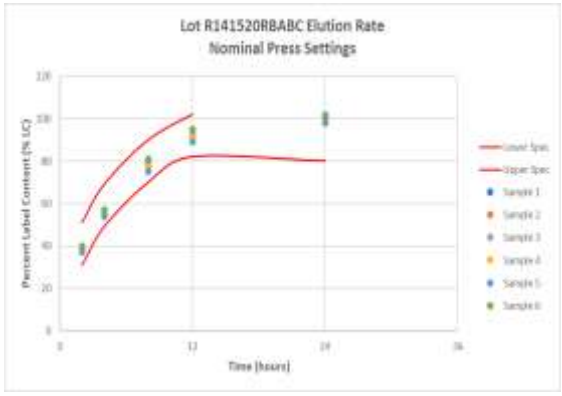

Figure 16

Elution Rate Results Chart

Build 3 High Settings: Results Summary

Below in Table 3 is presented the Electrode Ring MCRD Testing Results against the pharmaceutical acceptance criteria. In addition, in Figure 17 the elution testing results are presented in a Time Graph.

Table 3

Electrode Ring MCRD Testing Results (High Settings)

Lot Number	R141520RBGHJ		
Test Description	**Component**	**Result Value**	**Pass/Fail**
Description	Visual P/F	Pass	Pass
Identity	Percent Diff Sample from Standard	0%	Pass
	ID UV P/F	Pass	Pass
Content Uniformity / UPLC	Stage 1, Acceptance Value (AV) A	1.8	Pass
Assay / UPLC	Dexamethasone Acetate	101.9 % LC	Pass
Degradation Products	Total Impurities	0.4 %	Pass

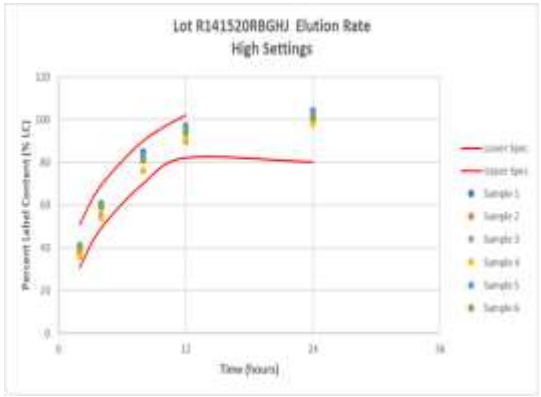

Figure 17

Elution Rate Results Chart

Elution rate results for all three builds are within specification and don't demonstrate any abnormal behavior.

The Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms *"Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation"* states in section 8 that "If a manufacturer wishes to use a manufacturing process that is not identical in every respect to the original manufacturing process used in the approved application, appropriate validation studies should be conducted to demonstrate that the new process is similar to the original process".

The 32-cavity mold uses same material of construction, same mechanisms of action, and same MCRD cavity dimensions as the 16-cavity mold. However, since the 32-cavity mold differs to the 16-cavity mold in terms of the number of cavities that each mold has, a f_2 In Vitro Dissolution Profile Comparison will be performed to establish correlation between the two molds. Model Independent Approach Using Similarity Factor: Dissolution profiles may be compared using the equation that defines a similarity factor (f_2).

The analysis was performed by individually comparing the 3 lots of Electrode Ring MCRD built in Experiment #1 against normal production lot R143713 refer to Table 4-6 for the comparison results. In addition, a fourth comparison was performed using the elution rate average of each timepoint of units tested throughout year 2020 against the elution rate results at nominal conditions built during Experiment #1 (Refer to Table 7).

Table 4
Similarity Factor Between 32 Cavity and 16 Cavity Mold (Low Settings Results)

Similarity Factor Between 32 Cavity and 16 Cavity Molds				
Timepoint (hr)	32 Cav	16 Cav	Difference	(Diff)^2
2	38.00	39.50	2	2
4	55.00	57.50	3	6
8	76.17	79.33	3	10
12	90.00	92.83	3	8
24	97.67	98.50	1	1
Sum of the Difference Square Root		27		
Similar Factor F_2		79.78345203		

Table 5
Similarity Factor Between 32 Cavity and 16 Cavity Mold (Nominal Settings Results)

Similarity Factor Between 32 Cavity and 16 Cavity Molds				
Timepoint (hr)	32 Cav	16 Cav	Difference	(Diff)^2
2	38.67	39.50	1	1
4	56.00	57.50	2	2
8	78.00	79.33	1	2
12	92.00	92.83	1	1
24	98.00	98.50	-1	2
Sum of the Difference Square Root		7		
Similar Factor F_2		90.34691179		

Table 6
Similarity Factor Between 32 Cavity and 16 Cavity Mold (High Settings Results)

Similarity Factor Between 32 Cavity and 16 Cavity Molds				
Timepoint (hr)	32 Cav	16 Cav	Difference	(Diff)^2
2	39.33	39.50	0	0
4	56.17	57.50	-1	0
8	80.67	79.33	-1	2
12	94.00	92.83	-1	1
24	101.50	98.50	-3	9
Sum of the Difference Square Root		13		
Similar Factor F_2		86.31037004		

Table 7
Nominal Conditions R141112R06 and Historical Data Average from Year 2020

Similarity Factor Between 32 Cavity and 16 Cavity Molds				
Timepoint (hr)	32 Cav	16 Cav	Difference	(Diff)^2
2	38.67	39.00	0	0
4	56.00	57.00	1	1
8	78.00	78.00	0	0
12	92.00	92.00	0	0
24	99.83	98.00	-2	3
Sum of the Difference Square Root		4		
Similar Factor F_2		93.07949696		

An f2 value between 50 and 100 suggests the two dissolution profiles are similar as established in the Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms "Scale-Up and Post approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation". For the three evaluated lots the f2 value is above 50 therefore they are considered equivalent.

- **Experiment #2:** *"Special Work Request (SWR) Report for Electrode Ring MCRD using 32-Cavity Mold to Evaluate Process Yield %"*

The purpose of this special work request was to explore different platen temperatures to determine

the setting that provided the highest theorical yield % using the 32-cavity mold.

The yield % results from build 1 to build 10 at Trim - Molded Ring MCRD are detailed in Table 8:

Table 8

Electrode Ring MCRD - 32 Cavity Mold - Yield Evaluation

Build	Yield %	Scrap Reasons
1	68.09%	**128 units** scrapped with code - MCRD_Part_Stuck_Mold_Cavity **1 unit** scrapped with code - MCRD_Embedded_FM **5 units** scrapped with code - MCRD_Missing_Material
2	95.71%	**16 units** scrapped with code - MCRD_Part_Stuck_Mold_Cavity **2 units** scrapped with code - MCRD_Embedded_FM
3	67.61%	**136 units** scrapped with code - MCRD_Part_Stuck_Mold_Cavity
4	24.76%	**314 units** scrapped with code - MCRD_Part_Stuck_Mold_Cavity
5	81.25%	**124 units** scrapped with code - MCRD_Part_Stuck_Mold_Cavity; **1 unit** scrapped with code - MCRD_Cuts
6	96.67%	**16 units** scrapped because created doubles from last run
7	83.96%	**21 bad units** due to low transfer pressure **50 units** scrapped with code - MCRD_Missing_Material
8	96.88%	**4 units** scrapped with code - MCRD_Part_Stuck_Mold_Cavity **8 units** scrapped with code - MCRD_Other; (MTM error while pulling the MCRDs out of the cavity **2 units** scrapped with code - MCRD_Embedded_FM **1 unit** scrapped with code - MCRD_Missing_Material;
9	98.13%	**9 units** scrapped with code - MCRD_Other; (MTM error while pulling the MCRDs out of the cavity
10	95.21%	**16 units** scrapped with code - MCRD_Missing_Material **6 units** scrapped with code - MCRD_Cuts **1 unit** scrapped with code - MCRD_Embedded_FM

Results Analysis

The pharmaceutical results for the three builds of Electrode-Ring, Radiused MCRD Part Number utilizing the 32-cavity mold and the current acceptable parameters for the Hot Transfer Press did not identify any practical significance between the groups and met all analytical requirements as per pharmaceutical testing criteria established in document "Steroid Lot Release Document for Electrode – Ring, Radiused MCRD".

Based on the results of process development report it is concluded that the current qualified Hot Transfer Press parameters for molding process can be used for both the 16-cavity mold and the 32-cavity mold to produce ring MCRDs that meet pharmaceutical testing acceptance. However, it was concluded that the ideal parameters, to maximize process yield, while still meeting acceptance criteria for pharmaceutical testing results are detailed in Table 9.

Table 9

Table 5 – Hot Transfer Press Ideal Parameters

Process Parameter	Setting Value
HP Clamp Pressure	22 tons
HP Transfer Pressure	6.0 tons
Ram Time	10 seconds
Clamp Time	105 seconds
Platen Temperature	245-255 °F
LP Clamp	90 psi
LP Transfer	60 psi

During this study all hot transfer press parameters were fixed at nominal conditions except for the platen temperature. The platen temperature was identified as a major contributor to the MCRD's shape, form, and visual criteria. Based on the results previously it was concluded that the current platen temperature parameters using the 32-cavity mold produce acceptable Ring MCRDs and complies with the manufacturing process yield minimum target metric for operations of 90% as the median yield of 96.19% over 1,860 parts built from Lot #R144212R05, R144212R01, R144212R14 and R144212R16 using a range of process parameters.

The Improve Phase was initiated with the implementation of the best solutions to address the root cause of the problem.

32 Cavity Mold Implementation

32 Cavity mold creates 2,000 parts from 250g of material, a 100% increase in material usage. Reduction of lots from 110 to 55 reduces cost of testing.

Expected Savings from 32-Cavity Mold Implementation.

- Decrease in Labor (hours mixing, milling, molding/FY)
  - From $360K to $90K (70% reduction)
- Decrease in burden cost (total cost of testing)
  - From $466K to $234K (50% reduction)
- Decrease in material expense (DXAC and Silicone cost)
  - From $666K to $333K (50% reduction)
- LBM/FY after implementation
  - From $1.5mil to $650K (56% reduction)

500 Cavity Peek Tray Implementation

The Anti-Static Black Peek Trays will be implemented as a process improvement initiative address the count discrepancy issue in the manufacturing line of the electrode ring MCRDs to enhance the inspections for the Electrode Ring MCRDs (Refer to Figure 18 for image of the 500 Cavity Peek Tray). The Anti-Static Black Peek are manufacturing aids to enhance the visibility of the MCRD rings during visual inspections and reduce movement of the MCRDs during the manufacturing process due to its anti-static properties.

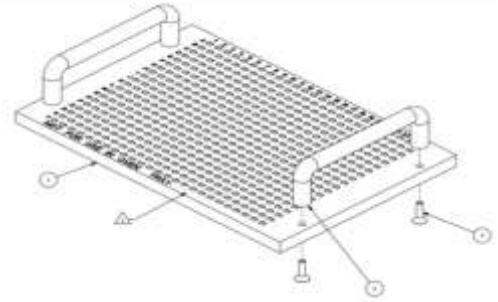

Figure 18
500 Cavity Peek Tray Drawing

The Control Phase consisted of implementing the process control and monitoring guidelines established by Medtronic.

General Requirements

Process Control and Monitoring is required for a production process to ensure the output of the process continues to meet specified requirements following validation. The Process Control and Monitoring determined during Process Development and Process Validation should be translated to the applicable manufacturing procedures, work instructions or plans.

Process Control and Monitoring is established during the Process Development (PD) phase. For outputs not fully verified, process control and monitors will be assessed and confirmed during Process Validation, through Operational Qualification (OQ) Run and Performance Qualification (PQ), to ensure specified requirements continue to be met for a process (es) post validation. Refer to Process Validation.

Quality Management System (QMS) processes e.g. Corrective and Preventive Action (CAPA), Risk Management, Post Market Surveillance (PMS), Nonconforming Reports (NCR), are quality indicators that are also used to confirm that specified requirements continue to be met post validation.

The Process and Control and Monitors that have been identified for a process are assessed and confirmed during OQ Run and PQ.

Process Control and Monitors in place during Process Validation activities are part of the validated process. Any changes to control and monitor requirements post validation may be considered process changes and will be assessed to determine the need for revalidation. QMS metrics may identify shifts in the process performance or unfavorable trends which require investigation and may warrant a review and/or update of Control and Monitor requirements.

All applicable Manufacturing Team Members responsible for the molding process per will be trained per the requirements in for Manufacturing Training). All training will be recorded in the appropriate Learning Management System (LMS).

CONCLUSION

In conclusion as part of the implementation of this Design Project for the Manufacturing of Electrode Ring – Monolithic Controlled Released Devices (MCRDs) the company will be benefits consist of the following:

- High scrap (99%) of raw material/high cost of testing - 32 Cavity mold creates 2,000 parts from 250g of material, a 100% increase in material usage. Reduction of lots from 110 to 55 reduces cost of testing.

- Units Count Discrepancy - New handling trays allow placement of 1 part in 1 well, easing counting activities and reducing monthly count discrepancy by 50%.
- Line not Balanced – After decreasing child lot size from ~950 to ~480 space in the WIP shelves and manufacturing stations was increased providing more flexibility for operators to support each other and reduce lead time.
- The Theorical Yield Percentage – will not be harmed as part of any of the improvement implementations. In addition, during testing runs the yield percentage was higher than the current yield percentage in the production line.

Overall savings for Medtronic Rice Creek Operations at Fridley as part of this design project are detailed in Table 10.

Table 10
Current vs. Future State LBM Yearly Savings

Current vs. Future State LBM Savings			
	Current State	Future State	Delta
Labor	$ 360,000.00	$ 90,000.00	$ 270,000.00
Burden	$ 466,000.00	$ 234,000.00	$ 232,000.00
Material	$ 666,000.00	$ 333,000.00	$ 333,000.00

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