



April 14, 2020

Food and Drug Administration
Center for Tobacco Products
Document Control Center (DCC)
Building 71, Room G335
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Michael W. Ogden, Ph.D.
Senior Vice President
Scientific & Regulatory Affairs

401 N. Main St.
Winston-Salem, NC 27101
336.741.5787
Fax: 336.728.7675
ogdenm@rjrt.com



RE: Premarket Tobacco Product Applications – Vuse Ciro ENDS Products

Dear Madam or Sir:

RAI Services Company, on behalf of R.J. Reynolds Vapor Company ("RJR")¹, hereby submits these Premarket Tobacco Product Applications ("PMTAs" or the "Applications") to the U.S. Food and Drug Administration ("FDA" or "the Agency"). RJR is seeking marketing orders under Section 910(c)(1)(A)(i) of the Federal Food, Drug, and Cosmetic Act ("FD&C Act" or the "Act"), as amended by the Family Smoking Prevention and Tobacco Control Act, for the Vuse Ciro Electronic Nicotine Delivery Systems (ENDS) products listed in Section A.3 below.² With this cover letter, RJR is submitting a complete group of PMTAs, organized according to the recommendations in FDA's 2019 Guidance for Industry (FDA, 2019).

Nine Vuse Ciro ENDS products are included in these Applications. The nine products include an ENDS component (the Vuse Ciro Power Unit), seven closed e-liquid cartridges (Vuse Ciro cartridges in seven flavors), and one ENDS co-package³ (Vuse Ciro Kit Original 1.5%). The Vuse Ciro Power Unit works in combination with all seven flavors of closed e-liquid cartridges.

The Company's testing of Vuse Ciro includes a range of scientific studies using well-known and established methodologies for the comparative assessment of tobacco products and associated health risks. The data and information submitted with these Applications include the results of product analyses, nonclinical health risk information, and human health and population health impact information, including the impact to both users

¹ RAI Services Company ("RAIS") is a wholly owned subsidiary of Reynolds American Inc. ("RAI") that coordinates regulatory compliance for RAI's subsidiary companies. Throughout these Applications, we refer to "RAIS" or "the Company." For clarity and ease of review, all of the following subsidiaries of RAI are included within these terms: (1) RAI Services Company, the legal entity that prepared and filed the Applications on behalf of its affiliated subsidiaries, which is responsible for the scientific research supporting the Applications; (2) R.J. Reynolds Vapor Company ("RJR"), the PMTA applicant and the legal entity responsible for marketing products under the Vuse brand; and (3) R.J. Reynolds Tobacco Company ("RJRT"), the legal entity responsible for providing analytical services and contract manufacturing of e-liquids, which is registered under Section 905 as the importer of record of the Vuse Ciro product.

² The products that are the subject of these Applications were originally marketed under the brand name "Vuse Solo+." The products were subsequently renamed to "Vuse Ciro" to avoid confusion in the market. See December 20, 2017 letter from Michael W. Ogden, Ph.D., RAI Services Company to the FDA CTP Document Control Center Re: Biannual Product Listing Update Pursuant to Section 905 of the Family Smoking Prevention and Tobacco Control Act.

³ On October 10, 2019, RAIS submitted PMTAs for Vuse Solo ENDS products that included, among 15 other products, two kits consisting of a co-packaged power unit and Original cartridge (Vuse Replacement Cartridge Original 4.8% G1 or G2). On October 30, 2019, FDA assigned STNs for the individual components (PM0000551, PM0000553–566), but did not assign STNs to the two kits. In these Applications, the Company is submitting PMTAs for the individual components of Vuse Ciro (i.e., the power unit and each cartridge) and one kit; however, RAIS understands the kit likely will not be assigned a separate STN based on the lack of assignment of STNs for the Vuse Solo kits.

Section A. General Information
RAI Services Company
Vuse Ciro PMTAs

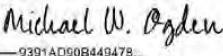
and nonusers of tobacco products. The results of these studies demonstrate that the marketing of these Vuse Ciro products is appropriate for the protection of the public health.

Based on the data and information included in these Applications, the Company requests that FDA issue orders authorizing the marketing of these Vuse Ciro products.

These Applications contain confidential commercial and non-public trade secret information belonging to the Company or its vendors and is exempt from public disclosure under 21 U.S.C. §§ 331(j) and 387f(c) and 5 U.S.C. §§ 552 (b)(4). We respectfully request that FDA maintain the confidentiality of the information in these Applications.

The Company appreciates FDA's careful consideration of these Applications and looks forward to working with the Agency to secure marketing orders under Section 910(c)(1)(A)(i) of the FD&C Act for the Vuse Ciro tobacco products discussed herein.

Respectfully,

DocuSigned by:


9391AD60B449478
Michael W. Ogden, Ph.D.
Senior Vice President – Scientific & Regulatory Affairs
RAI Services Company

Section A. General Information
RAI Services Company
Vuse Ciro PMTAs

Table of Contents

Table of Contents	3
Table of Tables	4
Table of Abbreviations	5
A. General Information	6
A.1 Company Name and Address	6
A.2 Authorized Contacts	6
A.3 New Product Identification	7
A.4 Prior Submissions for the New Product	11
A.5 Prior Meetings with FDA Regarding the New Product	11
A.6 Content Requirements of Section 910(b)(1) of the FD&C Act	11
A.7 Enclosures and Labeling Submitted with these Applications:	11
A.8 References	12

Section A. General Information
RAI Services Company
Vuse Ciro PMTAs

Table of Tables

Table A-1:	Listing of Vuse Ciro Unique Identifications.....	7
Table A-2:	Unique Identification - Vuse Ciro Power Unit.....	7
Table A-3:	Unique Identification - Vuse Ciro Cartridge Original 1.5%	8
Table A-4:	Unique Identification - Vuse Ciro Cartridge Menthol 1.5%	8
Table A-5:	Unique Identification - Vuse Ciro Cartridge Mint 1.5%	9
Table A-6:	Unique Identification - Vuse Ciro Cartridge Nectar 1.5%	9
Table A-7:	Unique Identification - Vuse Ciro Cartridge Melon 1.5%.....	9
Table A-8:	Unique Identification - Vuse Ciro Cartridge Tropical 1.5%	10
Table A-9:	Unique Identification - Vuse Ciro Cartridge Fusion 1.5%.....	10
Table A-10:	Unique Identification - Vuse Ciro Kit Original 1.5%.....	10
Table A-11:	Prior Meetings with FDA Relevant to Vuse Ciro	11
Table A-12:	PMTA Sections Corresponding to FD&C Act Section 910(b)(1) Requirements	11

Section A. General Information
RAI Services Company
Vuse Ciro PMTAs

Table of Abbreviations

ENDS	Electronic Nicotine Delivery Systems
FDA	U.S. Food and Drug Administration
PMTA	Premarket Tobacco Product Application
RAI	Reynolds American Inc.
RAIS	RAI Services Company
RJRT	R.J. Reynolds Tobacco Company
RJRV	R.J. Reynolds Vapor Company

Table of Contents

Table of Contents.....	1
Table of Tables.....	5
Table of Figures.....	10
Table of Abbreviations	11
H. Scientific Studies and Analyses	14
H.1 Design and Manufacturing.....	14
H.1.1 Components, Ingredients, and Additives.....	14
H.1.1.1 Finished Product – Aerosolizing Apparatus with E-liquid.....	14
H.1.1.2 Power Unit Components and Design.....	15
H.1.1.3 Cartridge Components and Design.....	24
H.1.1.4 Electrical Connections and Mechanical Interface	31
H.1.1.5 Product Design Failure Mode and Effects Analysis	35
H.1.1.6 Comparison with other ENDS Closed E-cigarettes	35
H.1.1.7 E-liquid Ingredients	36
H.1.1.8 Packaging	45
H.1.2 Principles of Operation	46
H.1.2.1 Connecting the Components.....	47
H.1.2.2 Operation of the Product.....	47
H.1.2.3 LED Indications During Use	47
H.1.2.4 Charging of the Power Unit.....	47
H.1.2.5 Features that Mitigate a Consumer’s Ability to Change the Product Characteristics	47
H.1.2.6 Features that Prevent Use of Vuse Ciro Power Units/Cartridges with Other Products	48
H.1.3 Manufacturing.....	49
H.1.3.1 RJRT Managerial Oversight	49
H.1.3.2 Employee Training.....	50
H.1.3.3 Supplier Qualification and Monitoring	50
H.1.3.4 Handling of Non-Conforming Products and Processes, Corrective Action Preventive Action, and Complaints.....	51
H.1.3.5 Manufacturing Overview	53
H.1.3.6 Manufacturing Processes and Testing Procedures	53
H.2 Properties.....	64
H.2.1 Aerosol Constituents	64
H.2.1.1 Aerosol Constituent Studies	65
H.2.1.2 Analytical Testing	67
H.2.1.3 Results	70
H.2.1.4 Published Studies in the Literature	79
H.2.1.5 Conclusions	79
H.2.2 E-liquid Properties	80
H.2.2.1 E-liquid Studies.....	80
H.2.2.2 Analytical Testing	81
H.2.2.3 Results	82
H.2.3 Stability	84
H.2.3.1 Stability Studies.....	84
H.2.3.2 Analytical Testing	85

H.2.3.3	Results	87
H.2.3.4	Conclusions	91
H.2.4	Extractables and Leachables	92
H.2.4.1	Extractables and Leachables Studies	92
H.2.4.2	Analytical Testing	94
H.2.4.3	Results	94
H.2.5	Thermal Profiling	96
H.2.6	Aerosol Particle Size Distribution	102
H.3	Nonclinical Studies	106
H.3.1	E-Liquid Ingredient Literature Review	106
H.3.2	Toxicological Assessment of Leachables	107
H.3.3	In vitro Toxicology Studies	110
H.3.3.1	Introduction	110
H.3.3.2	Ames Bacterial Reverse Mutation Assay	112
H.3.3.3	Neutral Red Uptake (NRU) Cytotoxicity Assay	113
H.3.3.4	In vitro Micronucleus (ivMN) Genotoxicity Assay	113
H.3.3.5	Overview of RAIS-Sponsored In vitro Study Designs and Methods	114
H.3.3.6	In vitro Studies of Vuse Ciro Aerosols	117
H.3.3.7	In vitro Studies of Vuse Solo G2 Aerosols	120
H.3.3.8	In vitro Studies of Vuse Solo G2 E-liquids	123
H.3.3.9	Summary of In vitro Toxicology Findings on Vuse Ciro Conducted by Other Researchers	125
H.3.3.10	Summary of In vitro Toxicology Findings	125
H.3.4	In vivo Toxicology Studies	126
H.3.5	Summary of the in vivo inhalational toxicity findings of the Vuse Solo G2 Original and Menthol ENDS Products	127
H.3.5.1	Vuse Solo G2 aerosols exhibit minimal in vivo inhalation toxicity that contrasts markedly with that of combustible cigarette smoke	127
H.3.5.2	In vivo Toxicology Studies of Vuse Solo G2	128
H.3.5.3	Overview of RAIS-Sponsored In vivo Study Designs and Methods	130
H.3.5.4	Conclusions – In vivo Studies	172
H.4	Clinical Studies	173
H.4.1	Introduction	173
H.4.2	Biomarkers of Exposure CSD170501	175
H.4.2.1	CSD170501: A Randomized, Controlled Study to Assess Biomarkers of Tobacco Exposure in Smokers During In-Clinic Confinement Switch to an Electronic Cigarette	181
H.4.2.2	Additional Analyses from CSD170501 Biomarker Study	185
H.4.3	Abuse Liability and Nicotine Pharmacokinetic Study CSD170401	187
H.4.3.1	CSD170401: A Single-Center, Randomized, Open-Label, Crossover Study to Assess Elements of Abuse Liability for Three Vuse Electronic Tobacco Vapor Products During an 11-Day Confinement	188
H.4.4	Nicotine Pharmacokinetic Study CSD170302	193
H.4.4.1	CSD170302: An Unblinded, Parallel, Randomized Study to Assess Nicotine Uptake in Smokers from Vuse Solo+ [Ciro] Electronic Cigarettes	193
H.4.5	Flavor Bridging Studies	196
H.4.5.1	CSD170303: An Unblinded, Parallel, Randomized Study to Assess Nicotine Uptake in Smokers from Vuse Solo Gen 2 Electronic Cigarettes	196

H.4.5.2	CSD170304: An Unblinded, Parallel, Randomized Study to Assess Nicotine Uptake in Smokers from Electronic Cigarettes and Combustible Cigarettes.....	198
H.4.5.3	CSD170301: An Unblinded, Parallel, Randomized Study to Assess Nicotine Uptake in Smokers from Vuse Vibe Electronic Cigarettes	200
H.4.6	Environmental Emissions Bridging Study	203
H.4.6.1	CSD1302: A Single-Center Evaluation of Environmental Emissions from Electronic Cigarettes and Tobacco-Burning Cigarettes.....	204
H.4.7	Summary of Clinical Studies.....	209
H.4.8	Conclusions	209
H.5	Population Health Effects	210
H.5.1	Survey Research	210
H.5.1.1	Analyses of Survey Data on Tobacco Use Behaviors	210
H.5.1.2	Demographic Characteristics and Tobacco Use History of Adult Vuse Ciro Users.....	211
H.5.1.3	Comparison of Vuse Ciro Users to Users of Other E-cigarettes	216
H.5.1.4	Comparison of Dependence on E-cigarettes and Combustible Cigarettes	220
H.5.1.5	Tobacco Use Transitions among E-cigarette Users	229
H.5.1.6	Use of Flavored Vuse Brand E-Cigarettes by Current and Former Adult Cigarette Smokers	235
H.5.1.7	Reduction in Cigarette Consumption with Dual Use of E-cigarettes.....	237
H.5.1.8	Young Adult E-cigarette Use Behaviors	242
H.5.1.9	Age Trends in Flavored E-cigarette Use among Young Adults	245
H.5.2	Consumer Testing (Likelihood of Use, Product Appeal, Risk Perceptions, and Label Comprehension Testing for Vuse Ciro)	248
H.5.2.1	Study Objectives.....	249
H.5.2.2	Survey Methodology	250
H.5.2.3	Results from Likelihood of Use Testing for Vuse Ciro	253
H.5.2.4	Interest in Available Flavors for Vuse Ciro.....	258
H.5.2.5	Results from Product Appeal Testing for Vuse Ciro	261
H.5.2.6	Results from Risk Perceptions Testing for Vuse Ciro.....	262
H.5.2.7	Results from Label Comprehension Testing for Vuse Ciro.....	268
H.5.3	Statistical Modeling of the Population Health Effects for Vuse Ciro.....	269
H.5.3.1	Overview of Statistical Modeling for Vuse Ciro	270
H.5.3.2	Statistical Modeling Projects a Population Health Benefit for Vuse Ciro.....	271
H.5.3.3	Analyses are Based on a Model with Demonstrated Validity	272
H.5.3.4	Modeling Accounts for a Wide Range of Unintended Harmful Changes in Tobacco Use	273
H.5.3.5	Vuse Ciro Modeling is Based on Empirical Data and Conservative Estimates	275
H.5.3.6	Sensitivity Testing Confirms a Projected Population Health Benefit for Vuse Ciro	280
H.5.3.7	Conclusion.....	281
H.6	Human Factors.....	282
H.6.1	Normal Use of the Products	282
H.6.2	Features that Mitigate the Potential for Misuse of the Products	282
H.6.3	Electronic Features of the Vuse Ciro Product that Mitigate Health Risks to the User or Nonuser.....	283
H.6.4	Features of the E-liquid Manufacturing Process and the Vuse Ciro Cartridge that Mitigate Potential Health Risks to the User and Nonuser	284
H.6.5	Product Information Provided to the Consumer Related to Product Use.....	284

H.6.6	Label Comprehension Assessment by Tobacco Users, Former Tobacco Users, and Never Tobacco Users	285
H.6.7	Vuse Ciro Usability Testing with Current Tobacco Users	285
H.6.8	Use-Related Hazards and Estimated Use Error Risk, Including Misuse	286
H.6.9	Adverse Experiences	286
H.7	References	287

Table of Tables

Table H-1:	Vuse Ciro Power Unit Components	17
Table H-2:	Vuse Ciro Power Unit Component Details	17
Table H-3:	Power Unit Design Parameters	23
Table H-4:	LED Status Indications	24
Table H-5:	Vuse Ciro Cartridge Components	26
Table H-6:	Vuse Ciro Cartridge Component Details	26
Table H-7:	Vuse Ciro E-liquid Fill Weights Target and Limits	31
Table H-8:	E-liquid Part Number by Product	36
Table H-9:	EL079 (Original)	36
Table H-10:	EL080 (Menthol)	37
Table H-11:	EL081 (Mint)	38
Table H-12:	EL083 (Nectar)	39
Table H-13:	EL084 (Melon)	39
Table H-14:	EL106 (Tropical)	40
Table H-15:	EL103 (Fusion)	41
Table H-16:	Formulation of Peach Flavor	42
Table H-17:	Formulation of Nat. & Art. Crisp Breeze FL. W.S. #12445	43
Table H-18:	Formulation of Strawberry Furanone 15% in PG	43
Table H-19:	Formulation of N&A Cocoa Flavor	44
Table H-20:	Packaging Materials of Vuse Ciro Power Unit	45
Table H-21:	Packaging Materials of Vuse Ciro Replacement Cartridges	45
Table H-22:	Packaging Materials of Vuse Ciro Kit	46
Table H-23:	Procedures and Work Instructions for Supplier Qualification and Monitoring	51
Table H-24:	Procedures, Work Instructions, and Documents for Non-Conformances	52
Table H-25:	Procedure for CAPA	52
Table H-26:	Procedures and Work Instructions for Complaints	53
Table H-27:	E-liquid Supplier Information	54
Table H-28:	Vuse Ciro E-Liquid Manufacturing Process	54
Table H-29:	Vuse Ciro E-Liquid Testing	55
Table H-30:	Procedures, Work Instructions, and Documents for Vuse Ciro E-liquid Manufacturing	55
Table H-31:	Cartridge and Finished Good Supplier	56
Table H-32:	Vuse Ciro Cartridge Assembly Process	57
Table H-33:	Vuse Ciro Testing of Current and Fill Weight	60
Table H-34:	Procedures, Work Instructions, and Documents for Vuse Ciro Cartridge Assembly	60
Table H-35:	Vuse Ciro Power Unit Assembly Process	61
Table H-36:	Procedures, Work Instructions, and Documents for Vuse Ciro Power Unit Assembly	61
Table H-37:	Vuse Ciro Replacement Cartridge Packaging Assembly Process	62
Table H-38:	Vuse Ciro Power Unit Packaging Assembly Process	62
Table H-39:	Procedures, Work Instructions, and Documents for Vuse Ciro Packaging Assembly Process	63
Table H-40:	FDA Recommended Constituents for Analysis in ENDS Aerosols	64
Table H-41:	Vuse Ciro Puffing Regimen Study	65
Table H-42:	Vuse Ciro Aerosol Constituent Studies	65
Table H-43:	Combustible Cigarette Comparator Smoke Constituent Study	66
Table H-44:	ENDS Market Comparator Aerosol Constituent Studies	66

Table H-45:	Glycidol and Propylene Oxide Analyses	67
Table H-46:	Mean E-liquid Formulation Constituent Levels and pH in Vuse Ciro Aerosol, Non-Intense Puffing Regimen	70
Table H-47:	Mean E-liquid Formulation Constituent Levels and pH in Vuse Ciro Aerosol, Intense Puffing Regimen	71
Table H-48:	Summary of Non-Formulation Constituents <LOD or <LOQ in All Vuse Ciro Aerosols, Non-Intense and Intense Puffing Regimens	72
Table H-49:	Mean Non-Formulation Constituent Levels in Vuse Ciro Aerosol, Non-Intense Puffing Regimen	73
Table H-50:	Mean Non-Formulation Constituent Levels in Vuse Ciro Aerosol, Intense Puffing Regimen	74
Table H-51:	Summary of Non-Formulation Constituents <LOD or <LOQ in All Vuse Solo G2 Aerosols, Non-Intense and Intense Puffing Regimens	75
Table H-52:	Mean Non-Formulation Constituent Levels in Vuse Solo G2 Aerosol, Non-Intense Puffing Regimen	76
Table H-53:	Mean Non-Formulation Constituent Levels in Vuse Solo G2 Aerosol, Intense Puffing Regimen	77
Table H-54:	Mean Glycidol Levels in Vuse Ciro Aerosol, Non-Intense Puffing Regimen	78
Table H-55:	ENDS Aerosol and Combustible Cigarette Smoke Acetyl Propionyl and Diacetyl Levels in Moldoveanu <i>et al.</i> (2017)	79
Table H-56:	Analyses of Vuse Ciro E-Liquids.....	81
Table H-57:	Mean E-liquid Formulation Constituent Levels and pH in Vuse Ciro E-liquids	82
Table H-58:	E-liquid Flavor Ingredient Inclusion Levels in Vuse Ciro E-liquids	82
Table H-59:	Mean Non-Formulation Constituent Levels in Vuse Ciro E-liquids	83
Table H-60:	Viscosity of Vuse Ciro E-liquids	83
Table H-61:	Vuse Ciro Aerosol Stability Studies	84
Table H-62:	Statistical Analysis for Vuse Ciro Aerosol Stability Studies	85
Table H-63:	Vuse Ciro Supplemental Aerosol Stability Study	85
Table H-64:	Vuse Ciro – Ranges [†] of Batch Means for E-liquid Formulation Constituents Measured in Aerosol from Time 0 to 12 Months Under Long Term Storage Conditions	87
Table H-65:	Vuse Ciro Original – Ranges [†] of Batch Means for E-liquid Formulation Constituents Measured in Aerosol from Time 0 to 12 Months Compared to Time 15 to 24 Months Under Long Term Storage Conditions	87
Table H-66:	Vuse Ciro – E-Liquid Formulation Constituents Measured in Aerosol at Time 24 Months Under Long Term Storage Conditions	88
Table H-67:	Vuse Ciro – Ranges [†] of Batch Means for Non-Formulation Constituents Measured in Aerosol from Time 0 to 12 Months under Long Term Storage Conditions Compared to Air Blanks and Combustible Cigarettes.....	89
Table H-68:	Vuse Ciro Original – Ranges [†] of Batch Means for Non-Formulation Constituents Measured in Aerosol from Time 0 to 12 Months Compared to Time 15 to 24 Months under Long Term Storage Conditions	90
Table H-69:	Vuse Ciro – Metals and Carbonyls Measured in Aerosol at Time 24 Months Compared to Combustible Cigarettes.....	91
Table H-70:	Vuse Ciro Cartridge Critical Components.....	92
Table H-71:	Extractables Studies of Vuse Ciro Critical Components.....	93
Table H-72:	Simulated Leachables Study in Artificial Saliva of the Vuse Ciro Mouthpiece	93
Table H-73:	Leachables Study of Vuse Ciro Cartridges.....	93

Table H-74:	Extractables and Leachables Summary for Vuse Ciro Replacement Cartridges	94
Table H-75:	Compounds Identified in 6-Month Accelerated Leachables Assessments of Vuse Ciro Aerosols	95
Table H-76:	Average ($\pm$ Standard Deviation) Maximum Temperatures ($^{\circ}$ C) for Vuse Ciro	101
Table H-77:	Puffing Regimens and Puff Groups Sampled for PSD Measurement of Vuse Ciro Aerosols	103
Table H-78:	Summary of Vuse Ciro MMAD (μ m) and (GSD) by Batch*	104
Table H-79:	Summary of Vuse Ciro Average MMAD (μ m) for All Batches by Regimen*	105
Table H-80:	Toxicological Assessment of Leachables in Vuse Ciro Aerosols	107
Table H-81:	Estimated Daily Inhalation Exposure to Leachables Compounds in Vuse Ciro Aerosols.....	107
Table H-82:	<i>In vitro</i> Studies of Vuse Ciro Aerosol	115
Table H-83:	<i>In vitro</i> Studies of Vuse Solo G2 Aerosol	115
Table H-84:	<i>In vitro</i> Studies of Vuse Solo G2 E-Liquids	115
Table H-85:	Machine Puffing Parameters for Aerosol Collection for Vuse Ciro <i>In vitro</i> Toxicology Studies	117
Table H-86:	Machine Puffing Parameters for Aerosol Collection for Vuse Solo G2 <i>In vitro</i> Toxicology Studies	117
Table H-87:	Ames Mutagenicity Results for Vuse Ciro Aerosol Total Particulate Matter (TPM) and Gas Vapor Phase (GVP)	118
Table H-88:	NRU Cytotoxicity Results for Vuse Ciro Aerosol Total Particulate Matter (TPM) and Gas Vapor Phase (GVP).....	119
Table H-89:	ivMN Genotoxicity Results for Vuse Ciro Aerosol Total Particulate Matter (TPM) and Gas Vapor Phase (GVP).....	120
Table H-90:	Ames Mutagenicity Results for Vuse Solo G2 Aerosol Total Particulate Matter (TPM) and Gas Vapor Phase (GVP)	121
Table H-91:	NRU Cytotoxicity Results for Vuse Solo G2 Aerosol Total Particulate Matter (TPM) and Gas Vapor Phase (GVP)	122
Table H-92:	ivMN Genotoxicity Results for Vuse Solo G2 Aerosol Total Particulate Matter (TPM) and Gas Vapor Phase (GVP)	123
Table H-93:	RAIS-Sponsored Nonclinical <i>In vivo</i> Toxicology Studies	129
Table H-94:	28-Day Vuse Solo G2 Original Study Design.....	133
Table H-95:	High Vuse Solo G2 Original Aldehyde Summary	133
Table H-96:	TK Parameters from Day 1 for Nicotine Following Inhalation Exposure with Vuse Solo G2 Original	135
Table H-97:	TK Parameters from Day 28 for Nicotine Following Inhalation Exposure with Vuse Solo G2 Original	135
Table H-98:	TK Parameters for Day 1 for Cotinine Following Inhalation Exposure with Vuse Solo G2 Original	135
Table H-99:	TK Parameters for Day 28 for Cotinine Following Inhalation Exposure with Vuse Solo G2 Original	135
Table H-100:	Incidence and Average Severity (Normalized to All Animals Examined, N=15) of Microscopic Findings Related to Vuse Solo G2 Original Exposure in Male Sprague Dawley Rats.....	136
Table H-101:	Incidence and Average Severity (Normalized to all animals examined, N=15) of Microscopic Findings Related to Vuse Solo G2 Original Exposure in Female Sprague Dawley Rats	137
Table H-102:	28-Day Vuse Solo G2 Menthol Study Design	139
Table H-103:	High Vuse Solo G2 Menthol Aldehyde Summary	139
Table H-104:	TK Parameters from Day 1 for Nicotine Following Inhalation Exposure to Vuse Solo G2 Menthol	141

Table H-105:	TK Parameters from Day 28 for Nicotine Following Inhalation Exposure to Vuse Solo G2 Menthol	141
Table H-106:	TK Parameters for Day 1 for Cotinine Following Inhalation Exposure to Vuse Solo G2 Menthol	141
Table H-107:	TK Parameters for Day 28 for Cotinine Following Inhalation Exposure to Vuse Solo G2 Menthol	141
Table H-108:	Incidence and Average Severity of (Normalized to all animals examined, N=15) Microscopic Findings Related to Vuse Solo G2 Menthol Exposure in Male Sprague Dawley Rats	143
Table H-109:	Incidence and Average Severity (Normalized to all animals examined, N=15) of Microscopic Findings Related to Vuse Solo G2 Menthol Exposure in Female Sprague Dawley Rats	143
Table H-110:	90-Day Vuse Solo G2 Original ENDS Study Design	145
Table H-111:	Weeks 4, 8, and 12 Combined - End of Exposure Plasma Nicotine and Cotinine Concentrations Following Inhalation Exposure with Vuse Solo G2 Original.....	147
Table H-112:	Incidence and Average Severity of Microscopic Findings in the Larynx Related to Vuse Solo G2 Original Exposure in Core and Recovery Males Annotated with Statistical Results	149
Table H-113:	Incidence and Average Severity of Microscopic Findings in the Larynx Related to Vuse Solo G2 Original Exposure in Core and Recovery Females Annotated with Statistical Results.....	149
Table H-114:	90-Day Vuse Solo G2 Menthol Study Design	151
Table H-115:	Weeks 4, 8, and 12 Combined - End of Exposure Plasma Nicotine and Cotinine Concentrations Following Inhalation Exposure with Vuse Solo G2 Menthol.....	153
Table H-116:	Summary of Notable Clinical Pathology Findings: Vuse Solo G2 Menthol	153
Table H-117:	Incidence and Average Severity of Microscopic Findings in the Larynx Related to Vuse Solo G2 Menthol Exposure in Core and Recovery Males Annotated with Statistical Results.....	155
Table H-118:	Incidence and Average Severity of Microscopic Findings in the Larynx Related to Vuse Solo G2 Menthol Exposure in Core and Recovery Females Annotated with Statistical Results	156
Table H-119:	90-Day Newport Gold Combustible Cigarette Study Design	158
Table H-120:	Weeks 1 and 13 C _{max} and AUC _{last} Values for Nicotine and Cotinine	160
Table H-121:	Carboxyhemoglobin (%) Measured in Weeks 4, 8, 12 in Males and Females	160
Table H-122:	Bronchoalveolar Lavage Fluid Parameters Measured on Day 92	161
Table H-123:	Incidence and Severity with Statistical Outcomes of Laryngeal Histopathological Findings in Male and Female Core and Recovery Rats Exposed to Newport Gold.....	162
Table H-124:	Incidence and Severity with Statistical Outcomes of Lung Histopathological Findings in Male and Female Core and Recovery Rats Exposed to Newport Gold	164
Table H-125:	Index of RAIS-Sponsored Clinical Studies	174
Table H-126:	Biomarkers of Exposure Evaluated in CSD170501	177
Table H-127:	Biomarker of Exposure Analytical Validations.....	178
Table H-128:	Biomarker Ability to Reliably Distinguish Smokers from Non-Smokers.....	179
Table H-129:	Half-Lives of Biomarkers of Exposure.....	180
Table H-130:	Publications and Presentations Related to CSD170501	186
Table H-131:	Publications and Presentations Related to CSD170401	192
Table H-132:	Cigarette Use History among Adult Current Established Vuse Ciro Users.....	213
Table H-133:	c-Statistics (increment over 0.50, the 'null' value) Comparing Profile of Vuse Solo Users to that of Users of Other E-cigarettes	218
Table H-134:	Comparison of Tobacco Use Histories and Demographic Characteristics of Established Users of Vuse Solo and Vuse Ciro, National Tobacco Behavior Monitor	219
Table H-135:	Comparisons of Cigarette Dependence and E-cigarette Dependence by Data Source	225

Table H-136:	E-cigarette Dependence among Adult Current E-cigarette Users Who Have or Have Not Stopped Smoking.....	226
Table H-137:	Cigarette and E-cigarette Dependence among Former Users of One or Both Products	227
Table H-138:	Use of Flavored Vuse Solo E-cigarettes by Smoking Status (TTM and NTBM).....	236
Table H-139:	Change in CPD from One Year Ago to Time of Survey among Dual Users versus Exclusive Smokers	239
Table H-140:	Reductions in CPD of 50% or More ¹ from One Year Ago to Time of Survey among Dual Users and Exclusive Smokers, NTBM and TTM.....	241
Table H-141:	Odds of Use of E-cigarettes and Vuse Solo by Age among Young Adults Ages 18-24, Total Tobacco Migration Tracker	243
Table H-142:	Odds of Use of E-cigarettes and Vuse Solo by Age among Young Adults Ages 18-24, National Tobacco Behavior Monitor	244
Table H-143:	Odds of Use of Flavored E-cigarettes by Age among Young Adults Ages 18-24, Total Tobacco Migration Tracker	246
Table H-144:	Odds of Use of Flavored E-cigarettes by Age Among Young Adults Ages 18-24, NTBM	247
Table H-145:	Interest in Each Available Flavor of Vuse Ciro by Tobacco User Group	259
Table H-146:	Weighted Mean Projected Product Use Rates for Adult Tobacco User Groups Based on Flavor of Most Interest.....	260
Table H-147:	Weighted Proportions of Correct Responses to Label Comprehension Questions by Tobacco User Group	269
Table H-148:	Summary of projections from ‘stacked’ cohort analyses, extrapolated to full U.S. population.....	272
Table H-149:	DPM(+1) Model Input and Supporting Data Sources	275
Table H-150:	DPM(+1) Input Values for Cigarette Smoking Initiation by DPM(+1) Age Category	276
Table H-151:	DPM(+1) Input Values for Smoking Cessation by DPM(+1) Age Category.....	276
Table H-152:	DPM(+1) Input Values for the Adoption of Vuse Ciro by DPM(+1) Age Category.....	278
Table H-153:	DPM(+1) Input Values for Transitioning to Vuse Ciro by DPM(+1) Age Category.....	279
Table H-154:	Percent of Respondents Completing Each Task Successfully for Vuse Ciro.....	286

Table of Figures

Figure H-1:	Vuse Ciro Power Unit.....	14
Figure H-2:	Vuse Ciro Cartridge.....	15
Figure H-3:	Accessory USB Charger.....	15
Figure H-4:	Nominal Dimensions, Assembled Vuse Ciro.....	15
Figure H-5:	Nominal Dimensions, Vuse Ciro Power Unit.....	15
Figure H-6:	Vuse Ciro Power Unit Detailed View.....	16
Figure H-7:	Vuse Ciro Power Unit Air Flow Path.....	21
Figure H-8:	Induced Pressure Differential During Puffing.....	22
Figure H-9:	Nominal Dimensions, Vuse Ciro Cartridge.....	24
Figure H-10:	Vuse Ciro Cartridge Detailed View.....	25
Figure H-11:	Vuse Ciro Cartridge Cross-Sectional View.....	26
Figure H-12:	Vuse Ciro Cartridge Air Flow Path.....	29
Figure H-13:	Vuse Ciro Cartridge E-liquid Flow Path.....	30
Figure H-14:	Vuse Ciro Cartridge Electrical-Mechanical Connector Cross-section.....	31
Figure H-15:	Vuse Ciro Power Unit Electrical-Mechanical Connector Cross-section.....	32
Figure H-16:	Vuse Ciro Electromechanical Block Diagrams.....	33
Figure H-17:	Accessory USB Charger Orientations.....	35
Figure H-18:	Single Cartridge Blister Package, Top and Bottom.....	46
Figure H-19:	Diagram Depicting the Thermocouple Locations on the Vuse Ciro Cartridge.....	97
Figure H-20:	Photograph Illustrating IR Camera Viewing Path to Nichrome Wire Heating Element.....	98
Figure H-21:	Photograph of a Representative Assembled, Modified Vuse Ciro Test Article.....	99
Figure H-22:	Example of a Thermal Profile (a single trial for the Vuse Ciro Flow Tube).....	100
Figure H-23:	Sham Control-Adjustment Flow Diagram.....	167
Figure H-24:	CSD170501 Study Design Schematic*.....	182
Figure H-25:	Mean Percent Changes in Constituent Urinary BoE Levels for Smokers Switched to Vuse Ciro Original or to Abstinence.....	184
Figure H-26:	CSD170401 Study Design Schematic.....	189
Figure H-27:	CSD170302 Study Design Schematic.....	194
Figure H-28:	CSD170303 Study Design Schematic.....	197
Figure H-29:	CSD170304 Study Design Schematic.....	199
Figure H-30:	CSD170301 Study Design Schematic.....	201
Figure H-31:	TWA _{8C} Nicotine Levels.....	206
Figure H-32:	TWA _{8C} Glycerin and PG Levels.....	207
Figure H-33:	TWA _{8C} Chamber Constituent Levels.....	208
Figure H-34:	Mean Projected Product Use Rates for Vuse Ciro among Tobacco User Groups and Subgroups.....	254
Figure H-35:	Weighted Mean Projected Product Use Rates and Purchase Intent Ratings for Vuse Ciro among Young Adults.....	257
Figure H-36:	Mean Ratings of Product Appeal for Vuse Ciro.....	261
Figure H-37:	Mean Ratings for Perceived Risk of Developing Generally Poorer Health with Vuse Ciro.....	263
Figure H-38:	Mean Ratings for Perceived Product Addictiveness with Vuse Ciro.....	265
Figure H-39:	Mean Ratings for Perceived Difficulty in Quitting Use of Vuse Ciro.....	267
Figure H-40:	Schematic representation of tobacco use transitions [beneficial transitions are represented by green color, and harmful transitions by red color].....	274

H. Scientific Studies and Analyses

H.1 Design and Manufacturing

H.1.1 Components, Ingredients, and Additives

FD&C Act §910(b)(1)(B) requires a full statement of the components, ingredients, additives, and properties, and of the principles of operation of new tobacco products. FDA interprets this statutory requirement to mean that applicants should provide a complete list of uniquely identified components, ingredients, and additives by quantity in each new product, as well as the applicable specifications and description of the intended function for each (FDA, 2019a).

H.1.1.1 Finished Product – Aerosolizing Apparatus with E-liquid

Vuse Ciro is an electronic nicotine delivery systems (ENDS) consisting of a power unit that works in combination with closed e-liquid cartridges. R.J. Reynolds Vapor Company ("RJRV") is the owner of the Vuse Ciro products and is responsible for product specifications and materials procurement. R.J. Reynolds Tobacco Company ("RJRT"), under contract with RJRV, manufactures the e-liquid in Vuse Ciro products.

The power unit and cartridges, manufactured by third-party suppliers, are not adjustable by the user. The closed design of the cartridges and the absence of adjustable parameters on the power unit and cartridges mitigate the potential for a consumer to change product characteristics, adjust product performance, or modify product ingredients. The power unit and cartridge use a metal screw thread connection with a precise screw thread length and a precise socket depth and shank length for the power unit and cartridge, respectively.

Vuse Ciro includes the following components and accessory:

- A rechargeable Vuse Ciro Power Unit (Figure H-1)
- A pre-filled Vuse Ciro Cartridge¹ (Figure H-2)
- An accessory USB charger for the power unit (Figure H-3)

Figure H-1: Vuse Ciro Power Unit



¹ "Replacement Cartridges" and "Cartridges" are used interchangeably throughout these Applications to describe the closed e-liquid cartridge component of the Vuse Ciro products. "Cartridges" is used to describe the cartridge in product labeling descriptions for Vuse Ciro.

Figure H-2: Vuse Ciro Cartridge

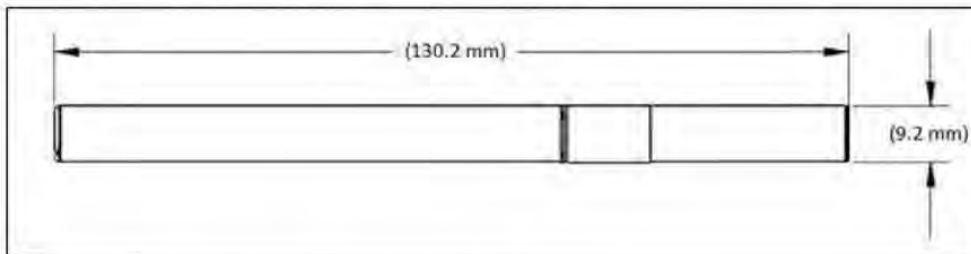


Figure H-3: Accessory USB Charger



Figure H-4 illustrates the nominal length and diameter of an assembled Vuse Ciro Cartridge and power unit.

Figure H-4: Nominal Dimensions, Assembled Vuse Ciro



H.1.1.2 Power Unit Components and Design

The section provides detailed technical descriptions of the Vuse Ciro Power Unit. The power unit is composed of several components and contains a rechargeable battery that powers the e-cigarette.

Figure H-5 shows a photo of the power unit with the overall nominal dimensions.

Figure H-5: Nominal Dimensions, Vuse Ciro Power Unit



H.1.1.2.1 Vuse Ciro Power Unit Components

Figure H-6 shows a detailed view of the power unit to illustrate each of the components.

Figure H-6: Vuse Ciro Power Unit Detailed View

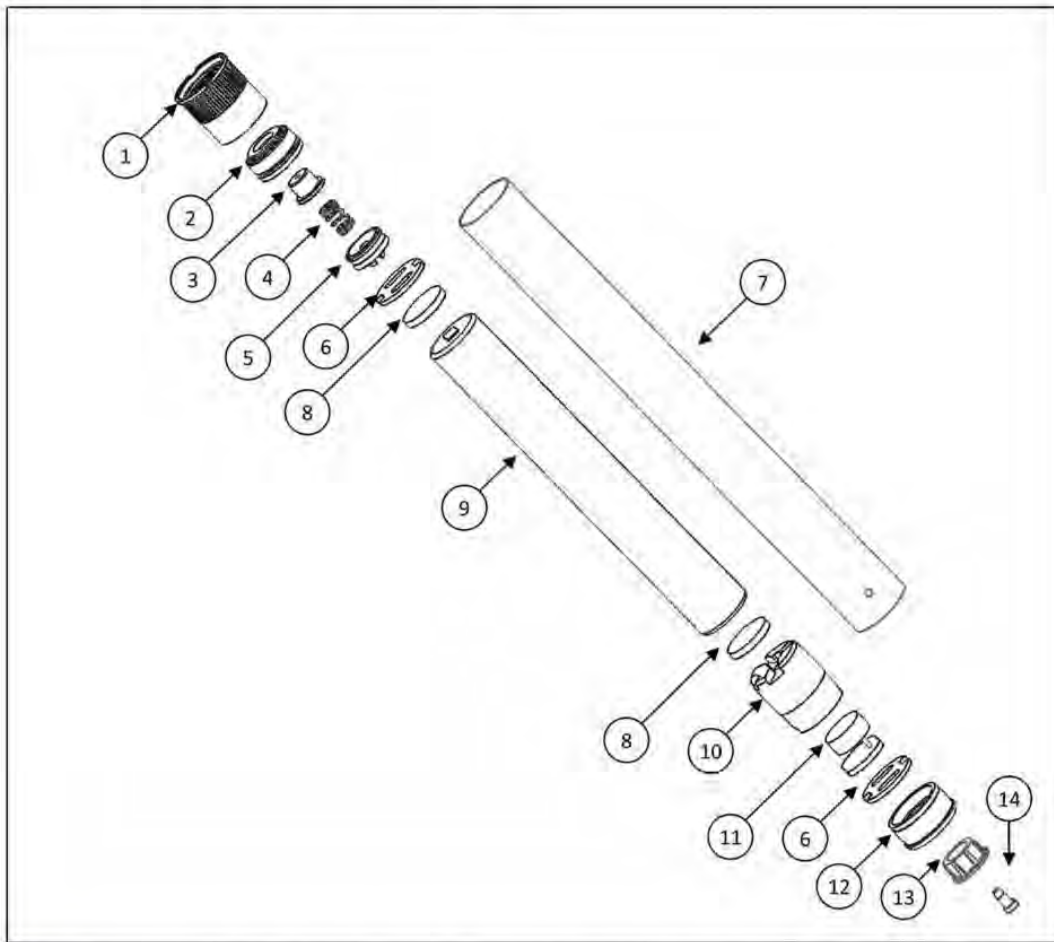


Table H-1 provides a description and material composition of each component of the Vuse Ciro Power Unit.

Table H-2 illustrates the component location within the assembly by shading in dark gray. A picture of each component is also provided (not to scale). The numbered labels in Figure H-6 correspond to the numbered rows in these tables.

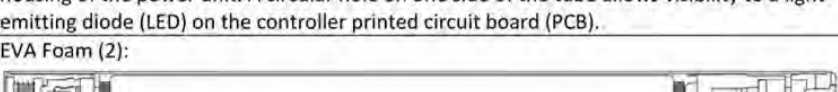
Table H-1: Vuse Ciro Power Unit Components

#	Name/Description	Material
1	Female Screw	Nickel-plated brass
2	Insulating Ring	Polyamide 66 (Nylon 66)
3	Positive Pin	Nickel-plated brass
4	Spring	Gold-plated steel wire
5	Electrode Ring Base	Nickel-plated brass
6	Spacers (2)	PET (polyethylene terephthalate)
7	Battery Tube	201 stainless steel
8	EVA Foam (2)	EVA (ethylene-vinyl acetate)
9	Battery Cell	Lithium-ion battery cell
10	Controller Base	Silicone
11	Controller	Electronic components, pressure sensor, wires
12	Bottom Ring	Nickel-plated brass
13	Flat Bottom	Polycarbonate/ABS (acrylonitrile butadiene styrene) plastic
14	Contact	Gold-plated brass
15	Glue (not shown)	Silicone adhesive
16	Tape (not shown)	Polyimide tape
17	Glue (not shown)	Methacrylate adhesive
18	Solder (not shown)	Lead-free solder

The total weight of the Vuse Ciro Power Unit is nominally 13.1 grams.

Table H-2: Vuse Ciro Power Unit Component Details

#	Location and Description	Physical Appearance
1	Female Screw:  The "Female Screw" is made from nickel-plated brass. The component acts as the power unit connector and engages the threads on the corresponding cartridge connector and forms part of the electrical circuit. There are four slots around the base to allow for inlet air flow at the power unit and cartridge interface.	
2	Insulating Ring:  The "Insulating Ring" is made from Polyamide 66. This component acts as an insulator between the female screw and positive pin.	

#	Location and Description	Physical Appearance
3	Positive Pin:  The "Positive Pin" is made from nickel-plated brass. This component forms part of the electrical circuit, contacting the positive pin in the cartridge assembly. The insulating ring aligns the positive pin to prevent contact with the female screw.	
4	Spring:  The "Spring" is a gold-plated steel spring. This component is part of the electrical circuit and provides proper engagement between the positive pin of the power unit and the positive pin of the cartridge assembly.	
5	Electrode Ring Base:  The "Electrode Ring Base" is made from nickel-plated brass. This component is part of the electrical circuit as the stationary component on the opposite side of the spring from the positive pin.	
6	Spacers (2):  The two "Spacers" are made from PET. These components help position other components within the power unit assembly.	
7	Battery Tube:  The "Battery Tube" is made from 201 stainless steel. This component serves as the outer housing of the power unit. A circular hole on one side of the tube allows visibility to a light-emitting diode (LED) on the controller printed circuit board (PCB).	
8	EVA Foam (2):  The two pieces of "EVA foam" are made from ethylene-vinyl acetate foam. One piece is placed at either end of the battery cell to cushion the battery relative to adjacent components.	

#	Location and Description	Physical Appearance
9	Battery Cell:  The "Battery Cell" is a 3.7 V (nominal) rechargeable lithium-ion battery. The battery is integrated into the product such that it is not accessible to and cannot be replaced by the consumer. The battery cell has been tested and conforms to the following standards: UN 38.3 IEC 62133:2012 UL 1642 For battery certifications, see Vuse Ciro Power Unit Battery Certifications	
10	Controller Base:  The "Controller Base" is made from silicone. This component positions the controller within the power unit and acts as a seal isolating the two faces of the pressure sensor.	
11	Controller:  The "Controller" is a commercial off-the-shelf PCB that drives the heater coil and regulates battery charging, among other functions. The controller PCB has a white LED and a pressure sensor component pre-wired as part of the assembly. The PCB has four connection points for the colored wires leading to other components in the power unit: (red) Battery Cell positive terminal (black) Battery Cell negative terminal, and female screw (blue) Electrode Ring Base (white) Contact	  
12	Bottom Ring:  The "Bottom Ring" is made from nickel-plated brass. This component serves as the end cap to the power unit. Two holes in this component allow air to enter the device to maintain the ambient pressure reference to one side of the pressure sensor. This component acts as the negative electrical connection during charging from the tip-end of the power unit.	

Most Confidential

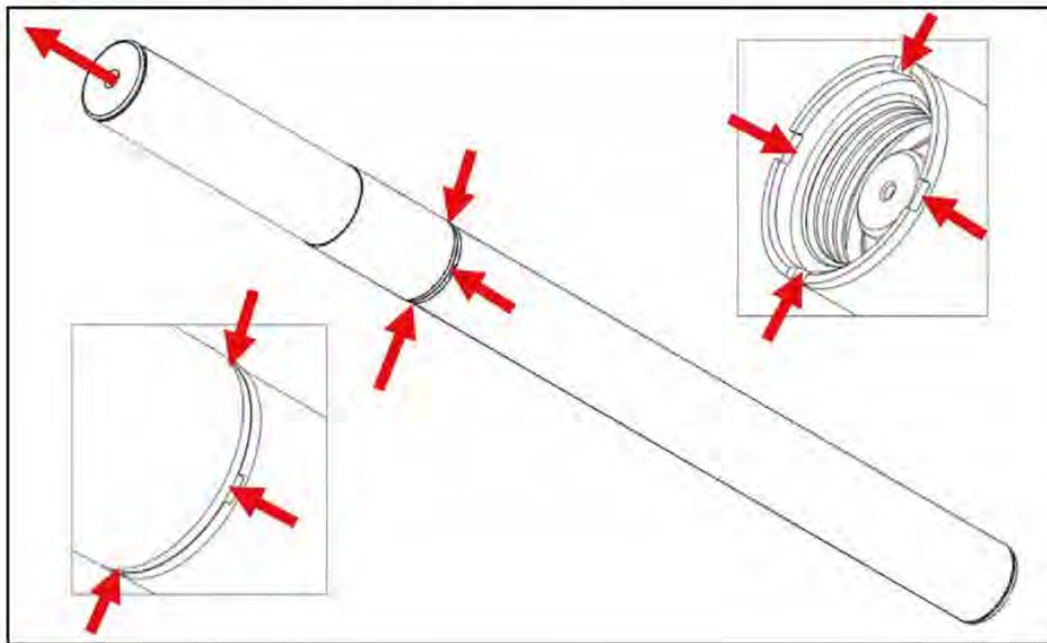
Page 19 of 310

#	Location and Description	Physical Appearance
13	Flat Bottom:  The "Flat Bottom" is made from polycarbonate/ABS plastic. This component acts as an insulator between the bottom ring and the contact.	
14	Contact:  The "Contact" is made from gold-plated brass. This component acts as the positive electrical connection during charging from the tip-end of the power unit.	
15	Silicone adhesive "glue" is used to adhere the controller wires to the controller base, ensuring that they remain connected during power unit assembly.	(not shown)
16	Polyimide tape locates the controller wires against the battery cell, ensuring that they remain in place during assembly and providing a secondary layer of insulation.	(not shown)
17	Methacrylate adhesive "glue" is used to adhere the female screw to the battery tube.	(not shown)
18	Lead-free "solder" is used to create electrical connections from the controller wires to the battery cell, female screw, positive pin, bottom ring, and contact.	(not shown)

H.1.1.2.2 Vuse Ciro Power Unit Air Flow Path

Figure H-7 shows the path of air through the product when air is drawn through the cartridge during use. Inlet airflow (red arrows) enters at four notches around the power unit connector and travels axially through the cartridge, exiting at the mouthpiece cap.

Figure H-7: Vuse Ciro Power Unit Air Flow Path



- A timer internal to the controller limits maximum puff length to 10 ± 2 seconds, at which time the power to the heater coil is shut off, and the white LED flashes twice. Following this event, there is a three-second period during which subsequent activation of the heater coil circuit is disallowed.
- LED Functions – The power unit controller drives the white LED indicator for all product operations. The LED indications are shown in [Table H-4](#).

Table H-4: LED Status Indications

LED status during Puffing	Device Status
White fade-in, fade-out	Puffing (heater active)
Flash 2 times	Max puff duration reached
On for 2 s	Short circuit detected
Flash 10 times	Battery depleted
LED status during Charging	Device Status
On	Charging
Flash 3 times	Disconnected while charging
Flash 20 times, then off	Fully charged

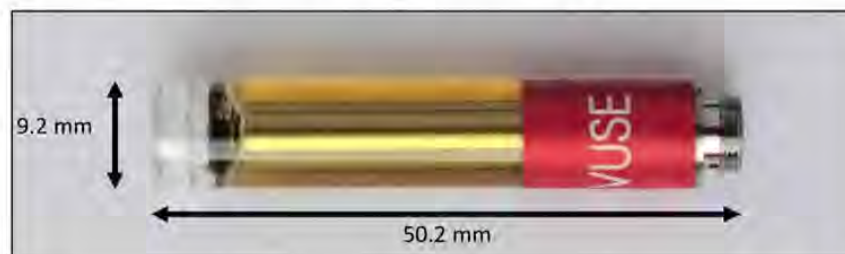
RJRV test procedures and data obtained for functionality assessment of the power unit features are included in [ID-0341 Vuse Ciro Functionality Testing Summary](#).

H.1.1.3 Cartridge Components and Design

Vuse Ciro replacement cartridges are closed e-liquid ENDS products currently marketed in two flavors (Original and Menthol) with five additional flavors included in these Applications. The cartridges are designed for a limited duration of use, and then must be replaced. The cartridges are not designed to be refilled or reused after the e-liquid is depleted.

[Figure H-9](#) shows a Vuse Ciro Cartridge and its overall nominal length and diameter. In this figure, the Original flavor variant is shown. Other flavor variants feature different colors on the label such that the consumer can quickly and easily distinguish between different flavors (see [Section E.1](#) for images of the labels for all Vuse Ciro Cartridges).

Figure H-9: Nominal Dimensions, Vuse Ciro Cartridge



H.1.1.3.1 Vuse Ciro Cartridge Components and Design

A single Vuse Ciro Cartridge design is shared among all Vuse Ciro flavors. The cartridge is composed of 13 component parts and contains the e-liquid (see Section H.1.1.7 for information regarding e-liquid composition).

A detailed view of the Vuse Ciro Cartridge is shown in Figure H-10 to illustrate each of the components that compose the cartridge. These components are described (by the labeled numbers) in the following sections. A cross-sectional view of the assembled Vuse Ciro Cartridge is shown in Figure H-11.

Figure H-10: Vuse Ciro Cartridge Detailed View

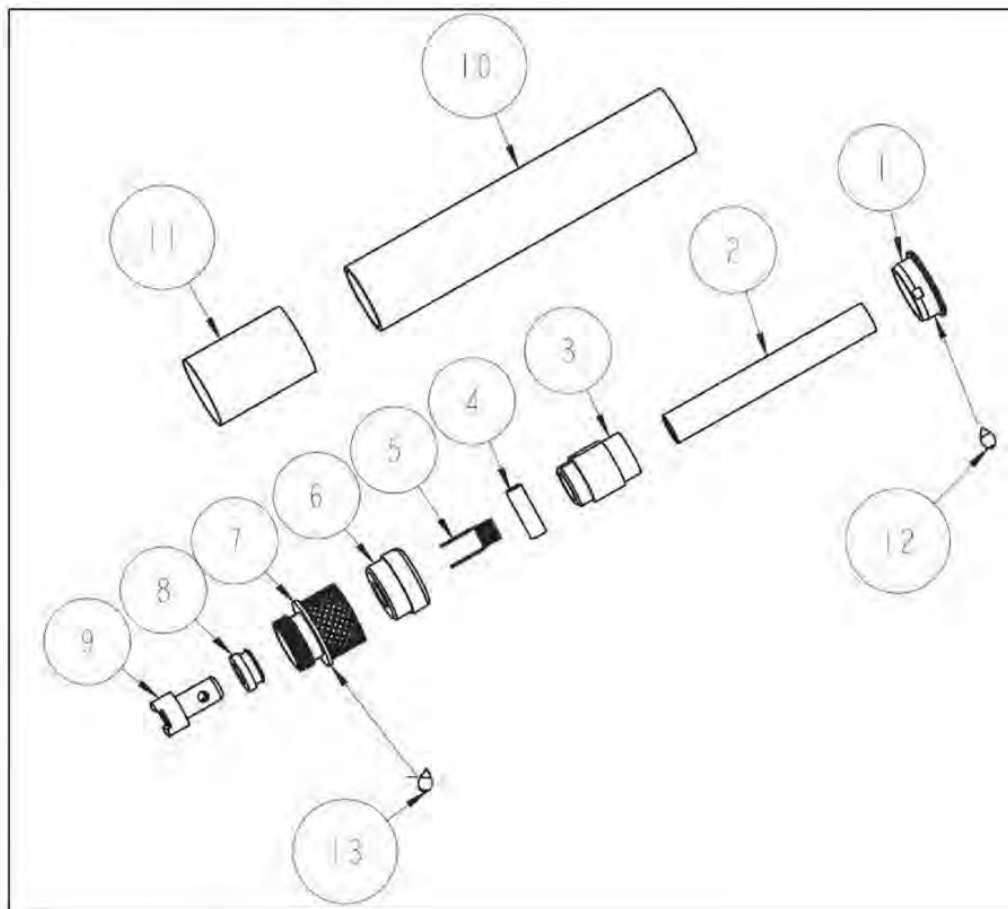


Figure H-11: Vuse Ciro Cartridge Cross-Sectional View

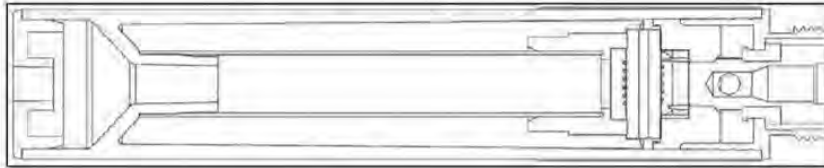


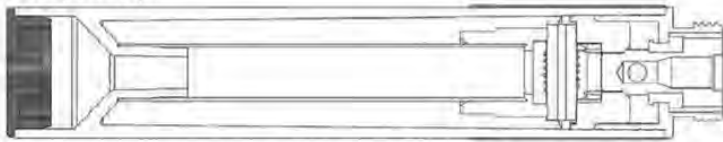
Table H-5 provides a description and material composition for each Vuse Ciro Cartridge component. The numbered labels in Figure H-10 correspond to the numbered rows in Table H-5.

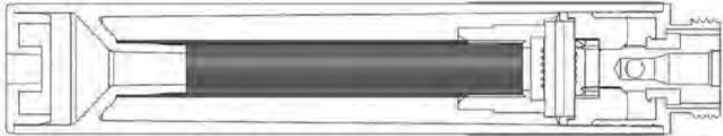
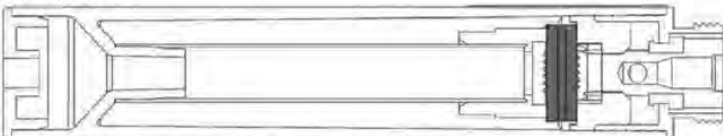
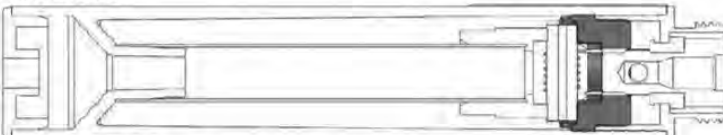
Table H-5: Vuse Ciro Cartridge Components

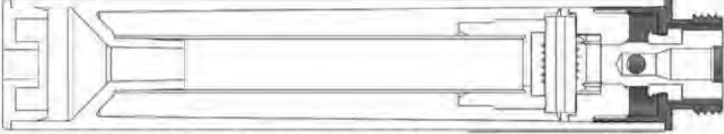
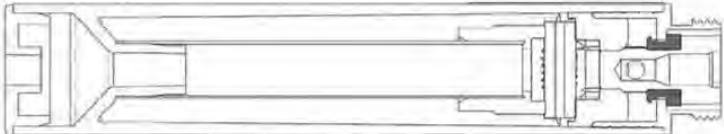
#	Name/Description	Material
1	Mouthpiece Cap	Tritan (copolyester)
2	Stainless Tube	304 Stainless steel
3	Sealing Silicone	Silicone
4	Ceramic Wick	Porous ceramic (alumina)
5	Heater	Nichrome wire
6	Silicone Base	Silicone
7	Male Screw	Nickel-plated brass
8	Insulating Ring	Silicone
9	Positive Pin	Nickel-plated brass
10	Plastic Cup	Tritan (copolyester)
11	Label	Polypropylene/polyester adhesive label
12	Epoxy	Epoxy resin adhesive
13	Glue	Cyanoacrylate adhesive

The total weight of the Vuse Ciro Cartridge is nominally 3.73 grams for the dry components plus the weight of the e-liquid. The e-liquid weight is approximately 1.06 g but varies slightly among flavors due to differences in the e-liquid formulations. Table H-6 provides a description of each component of the cartridge and illustrates the location within the cartridge assembly shaded in dark gray. A photo of each component (not to scale) is also provided.

Table H-6: Vuse Ciro Cartridge Component Details

#	Location and Description	Physical Appearance
1	Mouthpiece Cap:  The "Mouthpiece Cap" is made from Tritan. Aerosol is drawn through the hole at the center of the mouthpiece cap. The raised lip around the hole in the mouthpiece cap is intended to minimize the condensate from exiting the cartridge.	

#	Location and Description	Physical Appearance
2	Stainless Tube:  The "Stainless Tube" is made from 304 stainless steel. This component provides a flow path for aerosol to travel from the heater to the mouthpiece cap.	
3	Sealing Silicone:  The "Sealing Silicone" is made from silicone. This component prevents leakage of e-liquid from the reservoir into the airflow path. A recess in this component is used to seat the ceramic wick, which extends into the e-liquid reservoir (shown in light grey).	
4	Ceramic Wick:  The "Ceramic Wick" is made from porous (alumina) ceramic. This component absorbs e-liquid from the reservoir.	
5	Heater:  The "Heater" is made from nichrome wire with nickel wire leads spot welded to each side. This component is wrapped around the ceramic wick to form a coil. The heater coil produces the heat required to vaporize the e-liquid.	
6	Silicone Base:  The "Silicone Base" is made from silicone. This component positions the ends of the ceramic wick and the heater leads, and electrically insulates the leads from each other. Two slots in this component allow for airflow.	

#	Location and Description	Physical Appearance
7	Male Screw:  The "Male Screw" is made from nickel-plated brass. This component provides the mechanical connection between the cartridge assembly and the power unit. The male screw is also part of the heater circuit, making contact with one of the heater leads that protrudes from the silicone base. Two circular holes in this component allow for airflow.	
8	Insulating Ring:  The "Insulating Ring" is made from silicone. This component isolates the electrical circuit of the male screw from the positive pin.	
9	Positive Pin:  The "Positive Pin" is made from nickel-plated brass. This component is part of the heater circuit, making contact with one of the heater leads that protrudes from the silicone base. Two circular holes in this component allow for airflow.	
10	Plastic Cup:  The "Plastic Cup" is made from Tritan. This component acts as the outer body of the cartridge assembly and the e-liquid reservoir. The transparent outer wall allows visual observation of the e-liquid level.	
11	Label:  The "Label" is made from printed polypropylene and polyester with an adhesive backing. The label provides product branding and identifies the e-liquid flavor based on different accent colors (see Section E for more information on packaging and labeling, and Section E.1 for images of the labels for all Vuse Ciro Cartridges).	 (label, before application)

#	Location and Description	Physical Appearance
12	Epoxy: The "Epoxy" is an epoxy resin adhesive. This material is applied around the circumference of the mouthpiece cap to adhere it to the plastic cup.	(not shown)
13	Glue: The "Glue" is a cyanoacrylate adhesive. This material is applied around the circumference of the male screw to adhere it to the plastic cup.	(not shown)

H.1.1.3.2 Vuse Ciro Cartridge Air Flow Path

Figure H-12 shows the path of air (blue line) and aerosol (red dashed line) through the cartridge when air is drawn through the mouthpiece cap (upper right in figure).

Figure H-12: Vuse Ciro Cartridge Air Flow Path

