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Corner Case Strategy and Its Application in Medical Device Design Verification: A Case Study with Syringe Break Loose and Expulsion Force Testing

Xin Zhang
University of Northern Iowa

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In the medical device industry, design controls are an interrelated set of practices and procedures that are incorporated into the design and development process and must be followed in order to develop a product and commercialize it under regulated standards and regulations. Verification tests are an important step in the design controls. As these various systems and subsystems are designed, design verification testing methods are used to make sure that each design conforms to its own specifications. However, due to resource and budget availability, not every single presentation of the product family is tested in the verification phase. A corner case (or pathological case) involves a problem study or situation where products are tested in extreme environmental variables or operational conditions in order to verify the worst case of a product family and establish the confidence for the rest. In this paper, a test method to evaluate the syringe break loose and expulsion force is addressed, in which the corner case conditions for a syringe assembly were identified, the syringe assembly filled with medication solutions was tested, and the collected data were used to compare and leverage existing similar products. Minitab 17.0 was used to support the study and analysis.

Corner Case Strategy and its Application in Medical Device Design Verification: A Case Study with Syringe Break Loose and Expulsion Force Testing

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By

Xin Zhang

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Approved by:

Julie Zhang

Signature of Advisor (or reader) — Date: 11/1/2017

Ali E. Kashef

Signature of Second Faculty Professor — Date: 11/1/2017

Abstract

In the medical device industry, design controls are an interrelated set of practices and procedures that are incorporated into the design and development process and must be followed in order to develop a product and commercialize it under regulated standards and regulations. Verification tests are an important step in the design controls. As these various systems and subsystems are designed, design verification testing methods are used to make sure that each design conforms to its own specifications. However, due to resource and budget availability, not every single presentation of the product family is tested in the verification phase. A corner case (or pathological case) involves a problem study or situation where products are tested in extreme environmental variables or operational conditions in order to verify the worst case of a product family and establish the confidence for the rest. In this paper, a test method to evaluate the syringe break loose and expulsion force is addressed, in which the corner case conditions for a syringe assembly were identified, the syringe assembly filled with medication solutions was tested, and the collected data were used to compare and leverage existing similar products. Minitab 17.0 was used to support the study and analysis.

Keywords: medical device, design control, corner case analysis, break loose and expulsion force

Introduction

Purpose, Scope, and Summary of Objectives

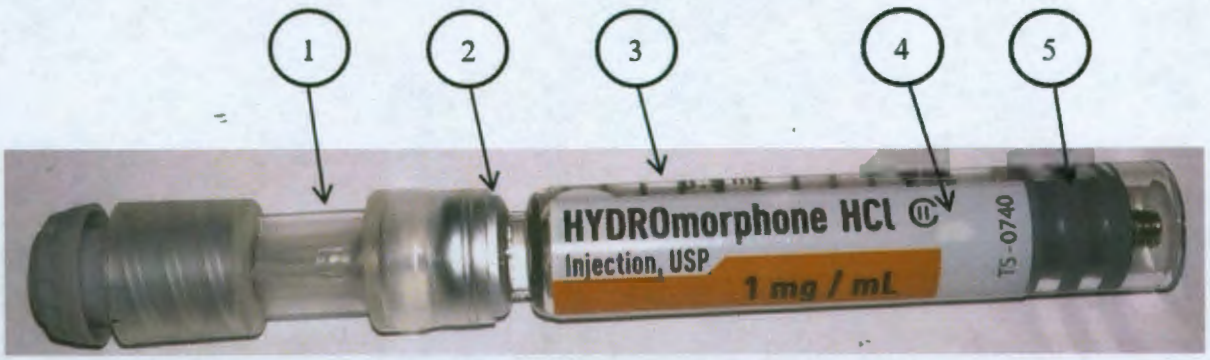
The purpose of this document is to capture the data analysis, rationale, and justification of substantiate sample selection for Design Verification testing of the Barracuda 1 mL prefilled syringe system, which is part of the design control management in the medical device product development life cycle. Design controls designate the application of a formal methodology to the conduct of product development activities. It is often mandatory (by regulation) to implement design control practice when designing and developing products within regulated industries, such as medical devices (Ogrodnik, 2013). Complex designs require more and different types of verification activities.

Background

Pre-filled syringes (PFS) are both the storage and the administration device for parenteral therapies, and they continue to increase in popularity due to their convenience, safety, and accuracy of drug delivery. As of 2012, PFS sales reached more than three billion units (Zhao, Lavalley, Mangiagalli, Wright, & Bankston, 2016). Prefilled syringes, such as the Carpuject Syringe, have gained wide acceptance since their introduction in the mid-1970s because they can be easily handled by healthcare professionals. They help to reduce the potential for medication errors by eliminating the need for nurses and doctors to calculate dosage, concentration, or volume and by minimizing mixing and handling errors. As one type of pre-filled syringe, the Barracuda 1 mL Syringe System consists of the 1 mL Cartridge Subsystem, shown in Figure 1, which is preassembled inside of the Cartridge Housing Assembly, shown in Figure 3. The Cartridge Subsystem is assembled and filled in an aseptic environment and then transferred to a separate room for final assembly with the Cartridge Housing Assembly.

The Carpuject Mini 1 mL Syringe System consists of the Carpuject Mini 1 mL Cartridge Subsystem, shown in Figure 2, which is manually placed by the user into the Carpuject Mini Holder Subsystem, shown in Figure 4. Since the Barracuda syringe shares the same pre-filled cartridge with Carpuject, which is an on-market product, the testing data of Carpuject is leveraged to help identify the corner case in design verification testing. A corner case (or pathological case) involves a problem or situation that occurs only outside of normal operating parameters—specifically one that manifests itself when multiple environmental variables or conditions are simultaneously at extreme levels, even though each parameter is within the specified range for that parameter. In this case, the combination of different medications, materials of rubber, and product lines of producing these syringes are the potential variables that may affect the functionality of syringes.

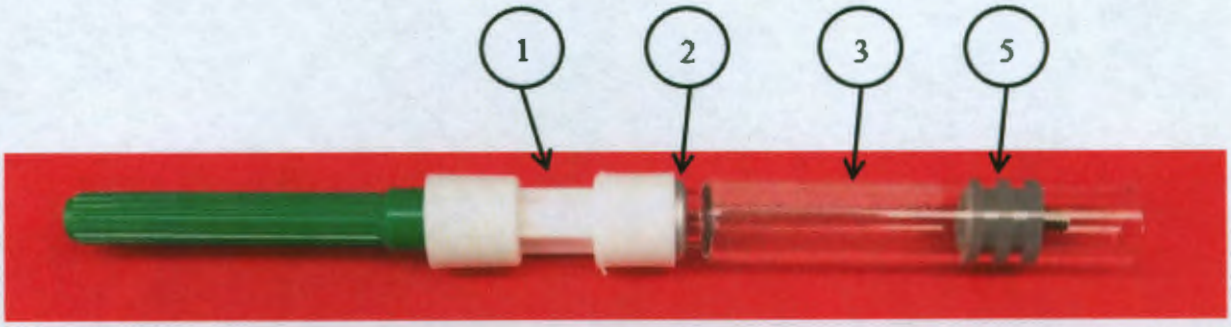
For each product of Barracuda and Carpuject, both cartridge subsystems use identical elastomeric closures (8-I seals and plunger stoppers) and glass cartridges. The metal cannula, which pierces the 8-I Seal upon activation, is identical in both luer lock systems.



①: Luer Lock System	②: 8-I Seal system	③: Glass Cartridge	④: Cartridge Label[1]	⑤: Plunger Stopper

[1] Draft label for representation purposes only.

Figure 1. Barracuda 1 mL Cartridge Subsystem

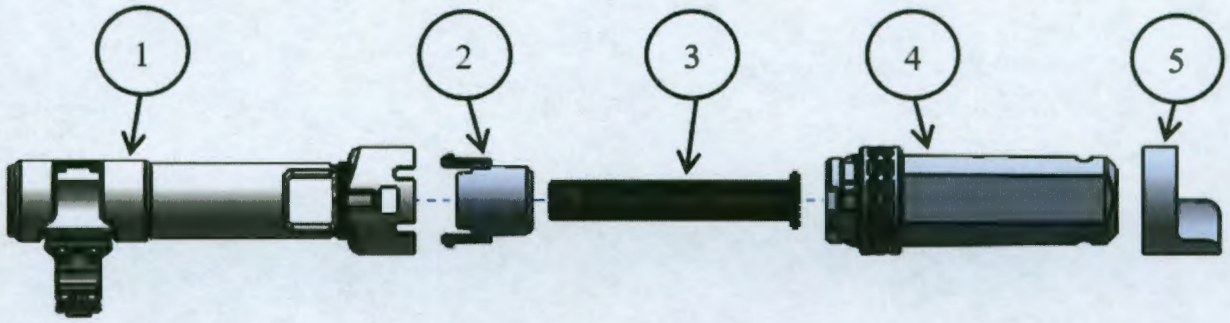


①: Luer Lock System	②: 8-I seal system	③: Glass Cartridge	④: Cartridge Label[2]	⑤: Plunger Stopper

[2] Representative labeling not shown.

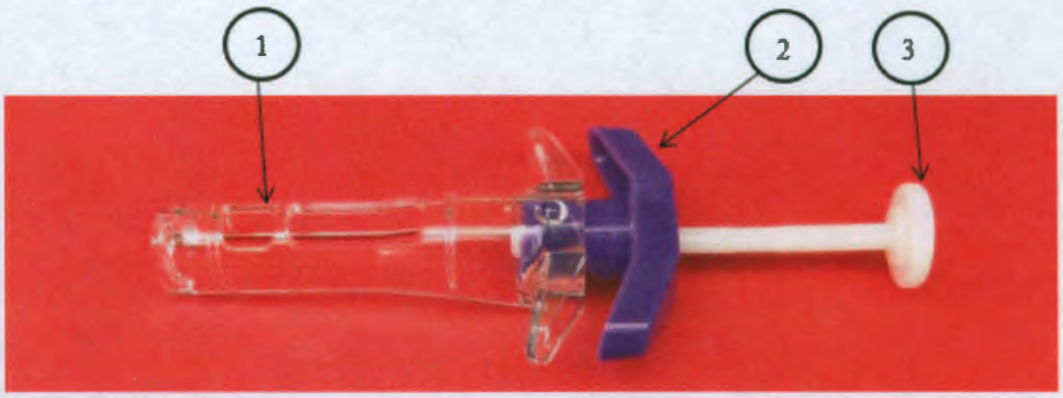
Figure 2. Carpuject Mini 1 mL Cartridge Subsystem

The Barracuda 1 mL Cartridge Housing Assembly is designed to activate the cartridge by rotation of the rear cover; as the rear cover is rotated, the driver is displaced axially, which activates the cartridge. Similarly, the Carpuject Mini holder is designed to activate the cartridge by rotation of the crank; once the cartridge is activated, the fluid path is created and is ready to deliver the medication. As the crank is rotated, it displaces axially and that leads to cartridge activation. Both systems operate on the principle of torque, and test results on one system will be proportional to the results on the other system. Thus, the worst case identified for the Carpuject Mini system would also be the worst case for the Barracuda system.



①: Cartridge Housing (Latch & Body)	②: Driver	③: Plunger Rod	④: Rear Cover	⑤: Rear Cover Label

Figure 3. Barracuda 1 mL Cartridge Housing Assembly



①: Holder	②: Crank	③: Plunger Rod

Figure 4. Carpuject Mini 1mL Holder

Break Loose and Expulsion Test Method

There are more than 30 test methods that could be performed in order to verify the performance and syringe ability of the Barracuda syringe system. Among these test methods,

some will be impacted by different drugs filled in the cartridge. In this paper, one of the most significant test methods, break loose and expulsion force, is studied to analyze the corner case. PFS systems essentially consist of a glass barrel made up of type I borosilicate glass that is typically siliconized for syringe functionality (Badkar, Wolf, Bohack, & Kolhe, 2011). Break loose force refers to the force required to break the stiction between the plunger and glass, while expulsion force refers to the force required to operate the plunger inside the glass/cartridge at a constant speed/force (ISO 11040-4, 2015). Expulsion force is also referred to as glide force in some articles. Both break loose force and expulsion force are measured on an Instron tester under a push speed of 100 mm/minute with a 100 N load cell. The method consists of two ramps. Ramp 1 is the initiating region, and Ramp 2 is the sustaining region.

Ramp 1: Apply compressive force for a length of 10 mm at breakaway crosshead speed. Record the maximum measured force (the value is the breakaway force).

Ramp 2: Apply compressive force at glide crosshead speed until the end length is reached (when 75% of the nominal fill volume is expelled). Record the peak measured force of this region (the value is the glide force).

Refer to Figure 5 for a detailed test setup and Figure 6 for the testing result example. Both of the forces shall not exceed 24.0 N when the plunger is pushed with 100 mm/min with fluid, per the design input requirement of Barracuda 1 mL syringe, DI-BAR-15 and DI-BAR-17. Statistical significance was defined as $P < .05$ (Rees, Lennartz, & Ignaut, 2015).

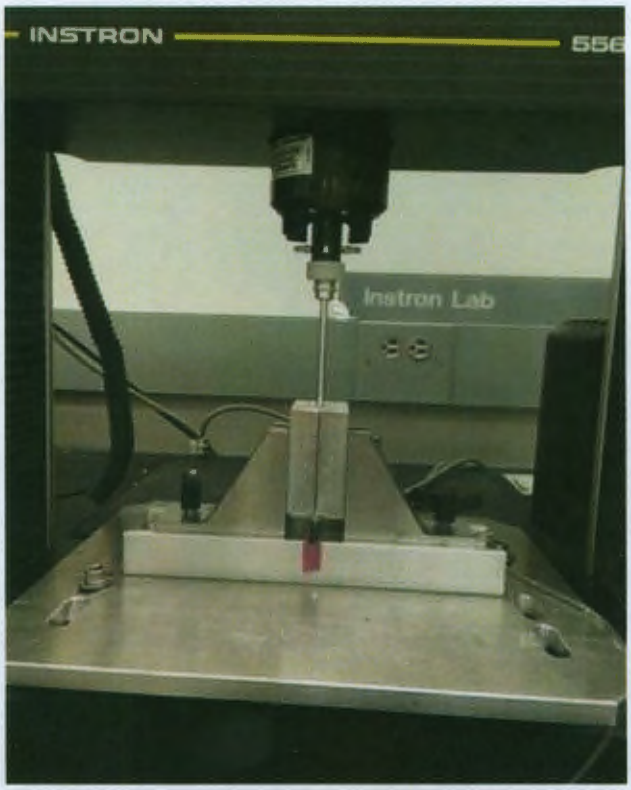
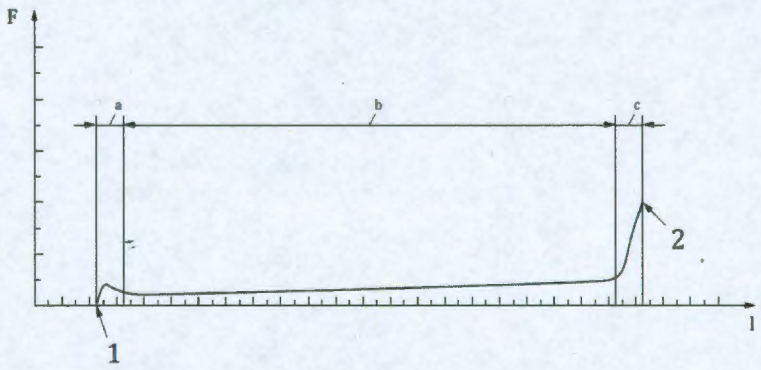


Figure 5. Test Setup for BLE testing



Key

1	start of stopper movement
2	end of testing condition
F	force in Newton
l	distance in millimetre
a	break loose region
b	glide force test region
c	end of stroke region

Figure 6. Illustration of BLE Test Result

Definitions, Acronyms, and Abbreviations

Terms and definitions used in this paper are as follows:

Term	Definition
BLE	Break Loose and Expulsion
DI	Design Input

Strategy to Define the Corner Case

Drug Portfolio and Primary Container Closure Configuration

The Barracuda 1 mL drug portfolio and associated primary container configurations are a subset of the drugs and primary container closure configurations of the Carpuject Mini Syringe System. The prefilled cartridges are the primary container closure for the drug products. The drug portfolio is defined in Table 1.

The purpose of verification testing by conducting break loose and expulsion force tests is to ensure the product can function as it is intended in a safe manner; specifically the two forces must not exceed a certain maximum value, which is specified in the design requirement document. Verification testing of break loose and expulsion force has been performed on the complete Carpuject Mini Syringe System in accordance with recommendations from the FDA Guidance in the publication *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products* from June 2013. The complete Carpuject Mini Syringe System, comprised of the prefilled drug cartridge and non-fluid path holder, was evaluated in accordance with the requirements of this guidance. Additionally, the system was evaluated according to the applicable recognized consensus standards for a Piston Syringe, as specified by 21 CFR 880.5860 (FDA 21 CFR 820.30, 1997). Since the system is a manual push

piston syringe, aspects such as the delivery flow rate and injection time are dependent on user preference. The Barracuda 1 mL syringe system has been evaluated similarly using the same guidance and syringe standards.

Table 1

Drug Portfolio

Drug Product	Concentration (per mL)	Total Strength (per total volume)	Currently Approved in the 1.5 mL Cartridge
Demerol	25 mg/mL	25 mg/1 mL	No
Demerol	50 mg/mL	50 mg/1 mL	No
Demerol	75 mg/mL	75 mg/1 mL	No
Demerol	100 mg/mL	100 mg/1 mL	No
Diphenhydramine	50 mg/mL	50 mg/1 mL	No
Heparin Sodium	10,000 Unit/mL	5,000 Units / 0.5 mL	Yes
Heparin Sodium	5,000 Unit/mL	5,000 Units / 1 mL	No
Hydromorphone	1 mg/mL	0.5 mg/0.5 mL	Yes
Hydromorphone	1 mg/mL	1 mg/1 mL	Yes
Hydromorphone	2 mg/mL	2 mg/1 mL	Yes
Hydromorphone	4 mg/mL	4 mg/1 mL	No
Ketorolac 30mg	30 mg/mL	30 mg/1 mL	Yes
Morphine	2 mg/mL	2 mg/1 mL	Yes
Morphine	4 mg/mL	4 mg/1 mL	Yes
Morphine	8 mg/mL	8 mg/1 mL	Yes
Morphine	10 mg/mL	10 mg/1 mL	Yes
Naloxone	0.4 mg/mL	0.4 mg/1 mL	No

Bracketing Approach

Bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size, and/or fill) are tested at all time points in a

full design (FDA Guidance for Industry, 2003). The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. A bracketing approach was used for performance testing of the Carpuject System whereby worst case drug product cartridges or water-filled cartridges were selected for testing based on the drug solution and component properties that have the potential to impact the performance of the syringe system.

In consideration of the direct overlap in drug portfolios and primary container closures, the Carpuject Mini bracketing approach and associated data were analyzed to further define the attributes known to impact the functional performance.

Table 2

Initial Assessment of Drug Attributes that Potentially Impact Device Features

Device Features	**Drug Attributes**					
	Solution pH	**Viscosity**	**Elastomer Formulation[3]**	**Plunger Height[1]**	**8-I Seal Thickness**	**Filling Line (Production Line)[2]**
Break Loose Force	Potential Impact	No Impact	Potential Impact	Potential Impact	No Impact	Potential Impact
Expulsion Force	Potential Impact	Potential Impact	Potential Impact	Potential Impact	No Impact	Potential Impact

[1] Note all plungers have the same outer diameter, thus only plunger height was considered as a drug attribute that required a bracketing approach.

[2] Filling line is the production line in which the glass cartridge is produced and prefilled with drug medications. The prefilled cartridge will then be transported to final assemble line to complete the assembly. This attribute has been added as potentially impacting attribute on device functionality after further data analysis of the verification work completed for Carpuject Mini.

[3] The material used to produce the rubber. Because some drug may require different rubber material in order to achieve high capability between drug and rubber, hence it is one potential factor that may influence the BLE force since different material may have different coefficient of friction.

Specific drug attributes were determined to impact break loose forces, expulsion forces, torque to activate, and leakage testing, and the justification for these impacts are provided in Table 3. Cells highlighted in gray indicate drug attributes that may have potential impact to device functionality as identified in Table 2.

Based on the assessment in Table 3, the break loose and expulsion forces (BLE) were assessed as potentially being impacted by some drug product solution characteristics. To determine if these drug attributes have a practical impact on the device functionality, data collected for the Carpuject Mini syringe system were analyzed.

Table 3

Initial Impact Rationale for Drug Attributes Impacting Device Features

Device Feature	**Drug Attribute**	**Rationale**
Break Loose Force	Solution pH	Extreme pH conditions may alter elastomeric materials under extreme chemical environments via absorption, extraction or chemical reaction. The pH could impact the elastomer and thus impact the interaction of the plunger with the glass cartridge. Therefore, the pH specification range for all drug formulations was bracketed.
	Viscosity	Viscosity is a resistance to fluid flow and would not cause resistance to the initial movement of the plunger within the glass cartridge, i.e., the break loose forces. Therefore this is no impact
	Elastomer Formulation	Any drug product interaction with an elastomeric closure may lead to a change in chemical properties of the elastomer. Therefore, all elastomeric formulations in the Carpuject Mini portfolio were bracketed.
	Plunger Height	The greatest plunger height has the highest surface area contact between the plunger and glass, and would represent the worst case to break stiction. Therefore, testing the greatest plunger height would represent the worst case and bracket smaller plunger heights.
	8-I Seal Thickness	Break loose forces are dependent on the relationship between the plunger and glass cartridge and the fluid properties that impact this relationship. Therefore, the 8-I seal thickness was not a necessary attribute to bracket for break loose testing.
	Filling Line	Difference in filling line processes may impact surface conditions of the components thus different filling lines could yield difference functional performance.

Device Feature	Drug Attribute	Rationale
Expulsion Force	Solution pH	Extreme pH conditions may alter elastomeric materials under extreme chemical environments via absorption, extraction or chemical reaction. Therefore, the pH specification range for all drug formulations was bracketed.
	Viscosity	A high solution viscosity may impact the force required to expel fluid from the cartridge. Therefore, testing the highest viscosity solution would represent the worst case and bracket drug products with lower viscosity drug solutions.
	Elastomer Formulation	Any drug product interaction with an elastomeric closure may lead to a change in chemical properties of the elastomer. Therefore, all elastomeric formulations in the Carpuject Mini portfolio were bracketed.
	Plunger Height	The greatest plunger height has the highest surface area contact between the plunger and glass, and would represent the worst case to expel fluid. Therefore, testing the greatest plunger height would represent the worst case and bracket smaller plunger heights.
	8-I Seal Thickness	Expulsion forces are dependent on the fluid and fluid path dimensions. Since the dimensions of the fluid path in the Carpuject Syringe System are dependent on the 22 gauge needle within the luer hub, which punctures the 8-I seal to produce a fluid path, the 8-I seal thickness was not a necessary attribute to bracket for expulsion testing.
	Filling Line	Difference in filling line processes may impact surface conditions of the components thus different filling lines could yield difference functional performance.
	Viscosity	Leakage from the cartridge units is dependent upon the critical dimensions between the glass cartridge and the elastomeric closures. The viscosity of the drug solution would not impact dimensions of these components.
	Elastomer Formulation	The elastomeric formulation may impact the interaction with the glass cartridge. All elastomeric formulations will be tested for leakage.
	Plunger Height	A smaller plunger height may have a reduced resistance to leakage, thus the smallest plunger height would bracket all other plunger heights.
	8-I Seal Thickness	A thinner 8-I seal thickness may have a reduced resistance to leakage, thus the thinnest 8-I seal will bracket all other 8-I seals.
	Filling Line	Leakage is based on the compression of the rubber 8-I seals and plungers against the glass. A change in surface conditions would not impact the amount the rubber can compress.

Rationale for Primary Container Closure Configuration Selection

An analysis of the drug product attributes provided in Table 2 was performed for each of the device features, and drug products given in Table 4 were selected as corner cases to bracket all of the drug products in the Carpuject Mini Syringe System. The Barracuda 1 mL portfolio is a subset of the Carpuject Mini portfolio and also utilizes the identical primary container closure system. This bracketing strategy for Carpuject Mini is summarized in Table 4 and is representative of the Barracuda 1 ml portfolio. The analysis in the subsequent sections of this document will evaluate the drug attribute impacts on the device functionality for the Barracuda 1 mL syringe system, and corner cases will be selected.

Analysis of Break Loose Force

Carpuject Mini break loose force testing required bracketing of the solution pH, elastomeric formulation, and plunger thickness. Configurations and drug products tested for Carpuject Mini are identified in Table 4 with light grey highlights. The analysis of Carpuject Mini data to follow will reassess the impact of the drug attributes for the Barracuda system. Carpuject Mini corner cases were selected, because the anticipated drug attributes impacting break loose forces were pH, plunger height, and elastomer formulation. Additional analysis of the Carpuject Mini data is provided herein that better defines the drug attributes that had practical impacts on the device functionality:

1. The drug product filling line also impacts break loose forces (not initially included in the Carpuject Mini assessment of drug attributes impacting device functionality).
2. pH of the drug solution has minimal impact on break loose forces

Table 4

Carpuject Mini Bracketing Strategy for Drug Product Attributes

Key: The lowest values in each attribute are highlighted in green and the highest in pink. The drug products that were tested are highlighted in light grey.

Drug Solution Attributes				**Plunger**			**8-I Cap Septum**		
Drug	**Total Strength / Volume**	**Viscosity (cp)**	**pH**	**Formulation**	**Height**	**Diameter**	**Formulation**	**Thickness**	**Diameter**
Fentanyl[1]	0.05 mg/mL	0.896	4.0-7.5	4023/50	.274 - .304"	.285 - .295"	4023/50	1.09 - 1.47mm	.312 - .340"
Naloxone	0.4 mg/mL	1.10	3.0-6.5	4405/50			4405/50		
Demerol	25mg/mL	1.03	3.5-6.0						
	50mg/mL								
	75mg/mL								
	100mg/mL								
Morphine Sulfate	2mg/mL,	1.09	2.0-4.5						
	4mg/mL								
	8mg/mL								
	10mg/mL								
Heparin Sodium	5,000 units/mL	1.69	5.0-7.5						
Hydro-morphine	0.5mg/0.5mL	1.80	3.5-5.5		.353 - .383"				
	1 mg/mL,								
	2 mg/mL,								
	4mg/mL								
Heparin Sodium	10,000 units/mL	2.76	5.0-7.5						
Diphen-hydramine	50 mg/mL	1.16	4.0-6.5	B5002-60N			B5002 60N	1.07 - 1.47mm	.310 - .338"
Buprenor-phine[1]	0.3mg/mL	1.23	3.5-5.5						
Ketorolac Trometh-amine	30mg/mL	1.29	7.2-7.6						

[1] This drug and primary closure are out of scope for the Barracuda 1 mL syringe but are identified here for comparison and analysis of Carpuject Mini data.

Break loose testing was performed for the Carpuject Mini syringe system using drug solution samples that were produced on medication filling lines (production lines) M19, TL, and CPM at the McPherson Manufacturing Facility. Barracuda 1 mL filling will only be performed

on the M19 line for final production. To estimate the contribution of the drug product impact on break loose force, Carpuject Mini data were analyzed to determine the impact of the filling line for samples manufactured on the CPM line.

Data from the Carpuject Mini design verification, characterization, and test method validation were utilized to capture the line variations across multiple lots and configurations; the difference between filling lines is readily apparent and shown in Figure 7. The pH range of products tested on each filling line is specified in Figure 7 and indicates that the variability of pH has minimal impact on break loose forces, while the filling line is a much stronger contribution to the break loose force. When the data are pooled for each filling line, the analysis presented in Figure 8 demonstrates that break loose forces of products manufactured on the CPM filling line are significantly different from forces of products manufactured on the M19 and TL filling line. ANOVA methodology is used to see the comparison mean of more than two group comparisons (Swati, Vipin, & Prakash, 2015).

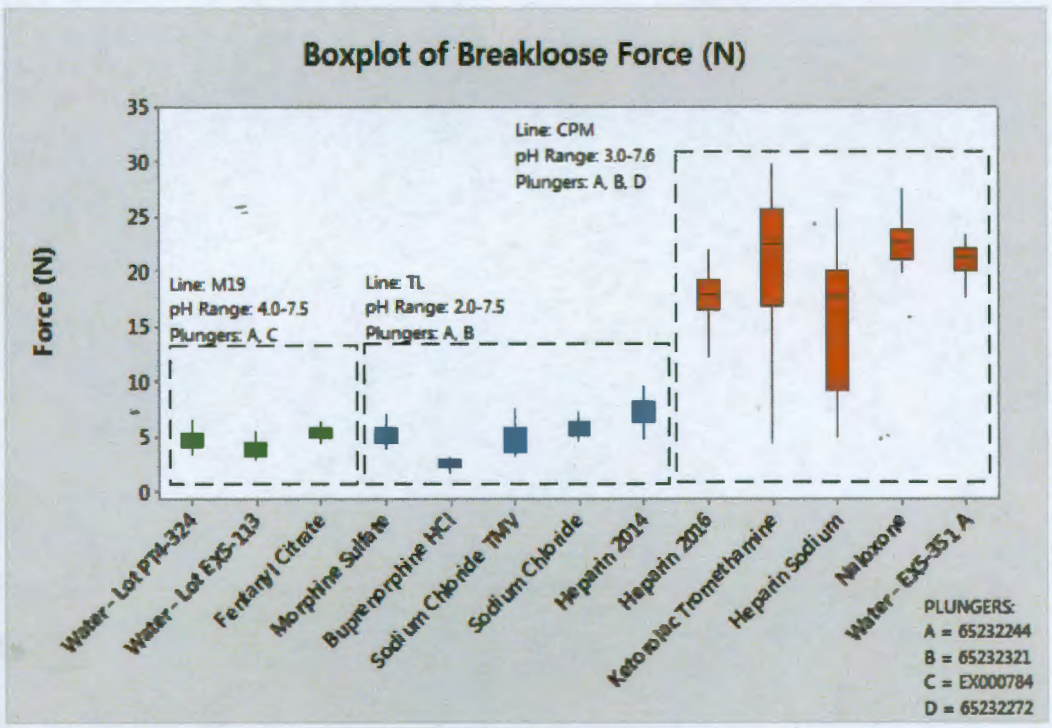


Figure 7. Break Loose Results Grouped by Filling Line

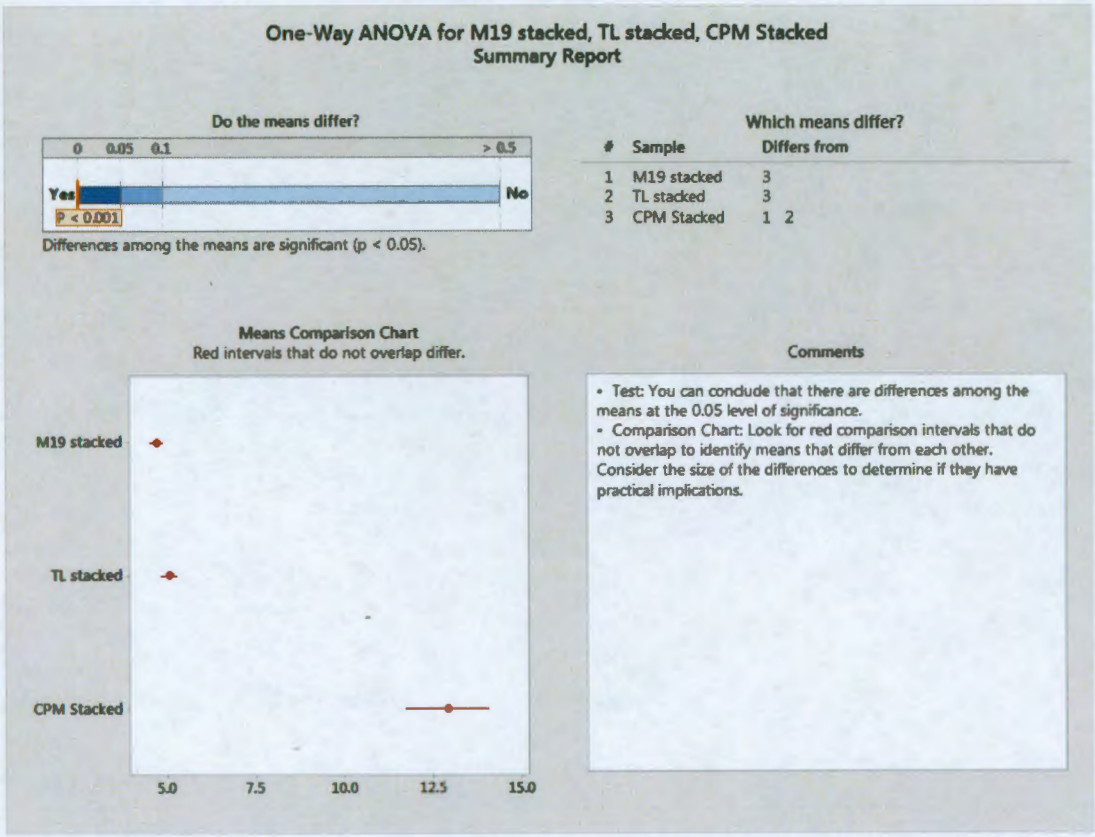


Figure 8. Difference in Break Loose Forces Using Pooled Data Sorted by Filling Line

In order to compare the Carpuject Mini data and understand the impact to the Barracuda 1 mL system, the existing CPM line data for Ketorolac Tromethamine and Naloxone was transposed to represent samples filled on the M19 line. The means were offset based on the difference in means between two identical configurations from the M19 line and the CPM line. The representative standard deviation of the M19 line was then applied to the transposed mean to generate a representative population, thus completing the transposition of the original data set to the M19 projection.

Based on water filled samples with identical configurations, the M19 break loose force is at least 15.452 N less than the CPM break loose force, as shown in Figure 9. Lot PT4-324 was produced on the M19 line using plunger 65232244; lot EX5-351 A was produced on the CPM line using plunger 65232244.

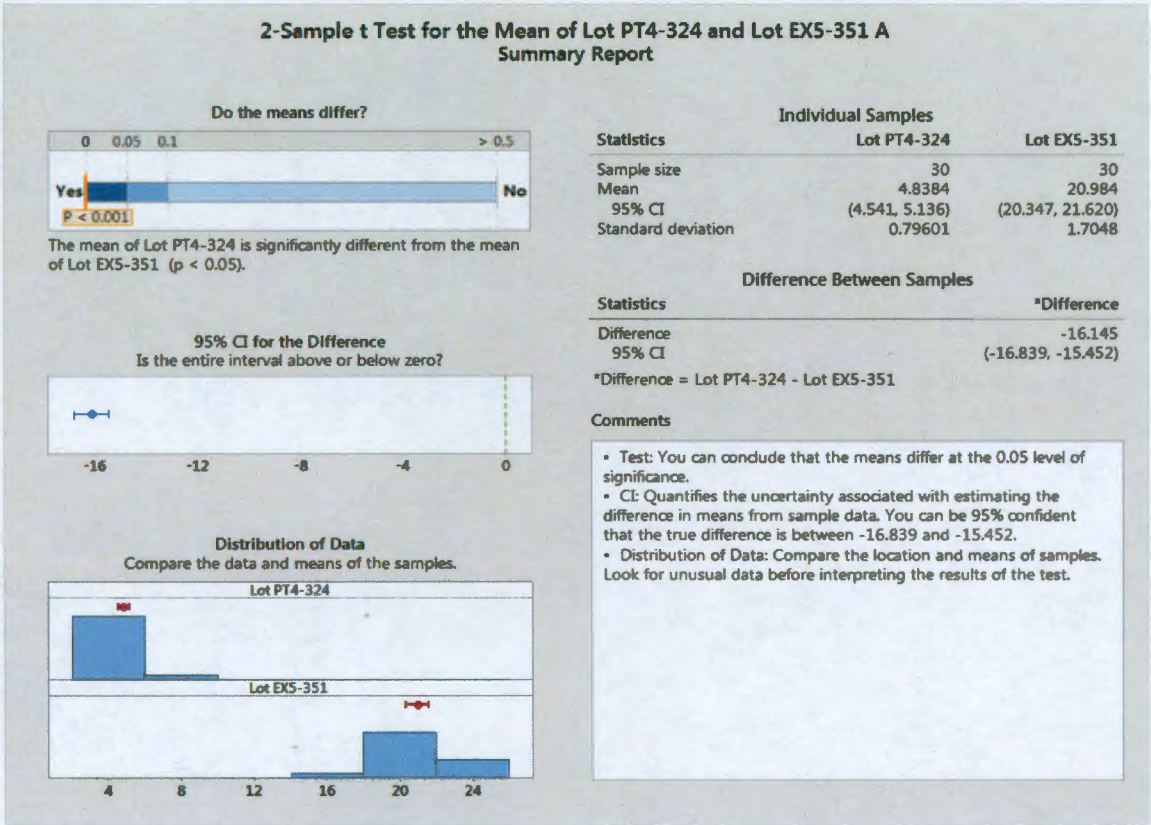


Figure 9. Difference in Mean between Identical Water-Filled Samples from Lines M19 and CPM

Ketorolac Tromethamine and Naloxone data were only available for product filled on the CPM line and therefore needs to be transposed for comparison to product filled on the M19 and TL lines. The difference between CPM and M19 break loose forces was applied as an offset to the measured means of Ketorolac Tromethamine and Naloxone; as shown in Table 5. Heparin Sodium will not be offset since data are already available from the TL line to support the analysis, and there was no statistical difference between the data for drug products filled on M19 and TL (see Figure 8).

Table 5

Mean Break Loose Forces Offset from CPM to M19

	Ketorolac	Naloxone
Original Mean from CPM (N)	20.468	22.625
Offset (N)	-15.452	-15.452
Transposed Mean for M19 (N)	5.016	7.173

Since there is no statistical difference between M19 and TL, the combined data from M19 and TL were treated as one population to maximize the number of data points and variability, yielding the worst case standard deviation to apply to the offset means of products manufactured on CPM. Figure 10 shows the standard deviation of the combined data from M19 and TL is 1.637 N. This standard deviation is applied to the offset means shown in Table 5.

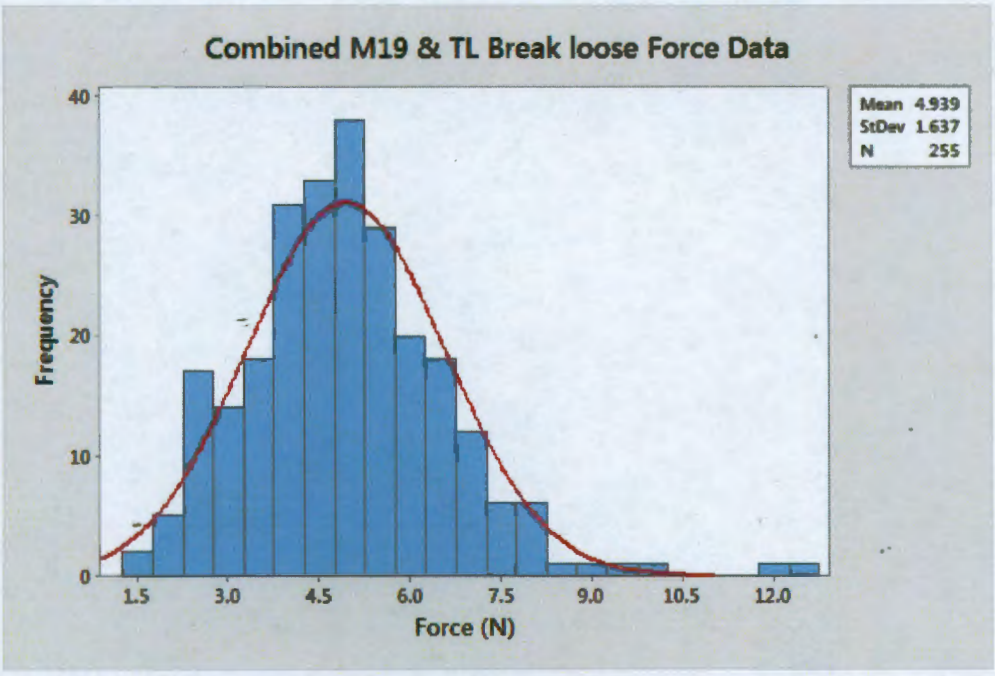


Figure 10. Combined Standard Deviation of Break Loose Forces from Samples from M19 and TL

The pooled standard deviation of M19 and TL is applied to the transposed means, and the projected populations are shown in Figure 11. The Ketorolac Tromethamine and Naloxone populations represent the anticipated break loose forces if they were filled on M19.

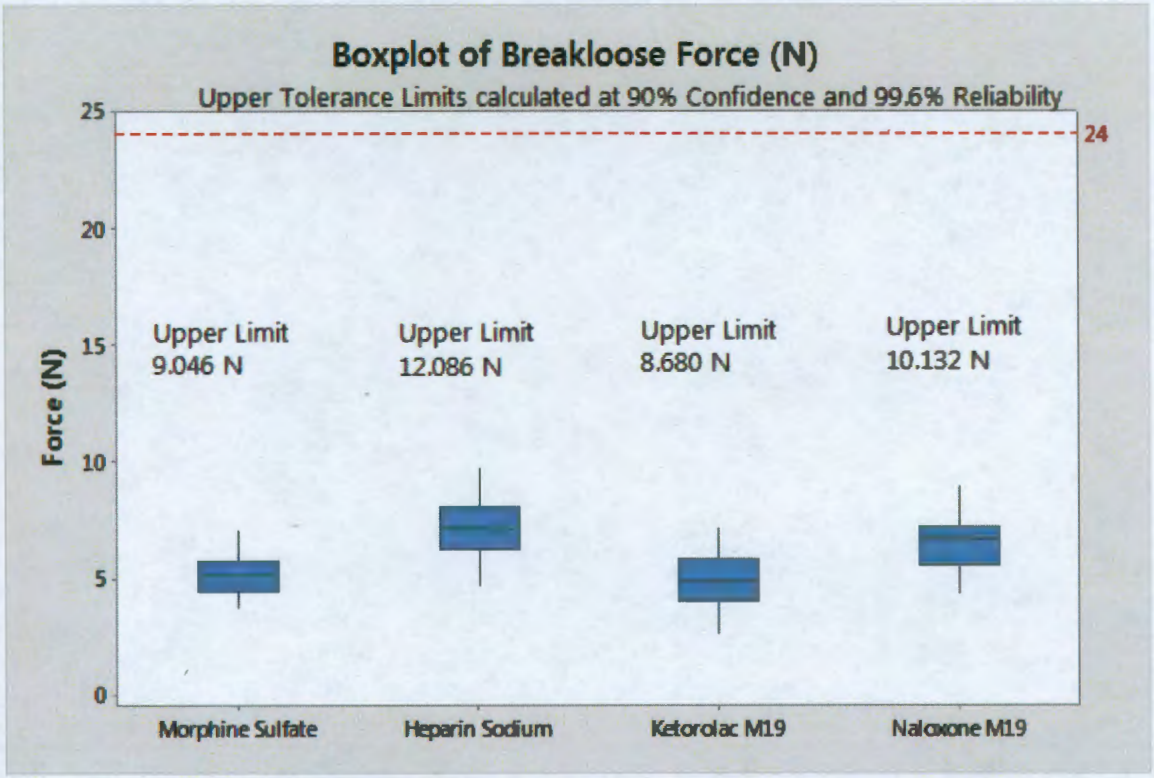


Figure 11. Boxplot of Applicable Drugs for the Barracuda 1 mL Portfolio and Upper Tolerance Limits

The upper tolerance limits for all drug groups are shown in Figure 11, and they all meet the Barracuda requirement of 24.0 N per DI-BAR-15, because the higher the break loose is, the more difficulty the user will face when operating the syringe. Heparin Sodium has the highest upper tolerance limit and thus presents the worst case for the primary cartridge configuration. Design verification will use water-filled cartridges using the elastomeric closures for the Heparin Sodium configuration. These cartridges will be fully assembled in the Barracuda cartridge housing assembly to demonstrate that the functional performance of the worst case configuration, in its final device assembly, meets the design requirement.

Analysis of Expulsion Force

Carpuject Mini expulsion force testing required bracketing of the solution pH, viscosity, elastomeric formulation, and plunger thickness. Configurations and drug products tested for Carpuject Mini are identified in Table 4 with light grey highlights. The analysis of Carpuject Mini data will assess the impact of the drug attributes for the Barracuda system.

Carpuject Mini corner cases were selected because the anticipated drug attributes impacting expulsion forces were pH, viscosity, plunger height, and elastomer formulation. Additional analysis of the Carpuject Mini data is provided herein that better defines the drug attributes that had practical impact to the device functionality:

1. The drug product filling line does not impact expulsion forces (not initially included in the Carpuject Mini assessment of drug attributes impacting device functionality)

2. pH of the drug solution has no impact on expulsion forces

3. Viscosity of the drug solution has no impact on expulsion forces

Expulsion force testing with these drug products was performed for the Carpuject-mini syringe system. Carpuject Mini test data were collected using samples (syringes filled with drug solutions) that were produced on filling lines M19, TL, and CPM. Barracuda 1 mL filling was only performed on the M19 line for final production.

Data from Carpuject Mini design verification, characterization, and test method validation were utilized to capture the line variation across multiple lots and configurations; Figure 12 does not show readily apparent differences between filling lines.

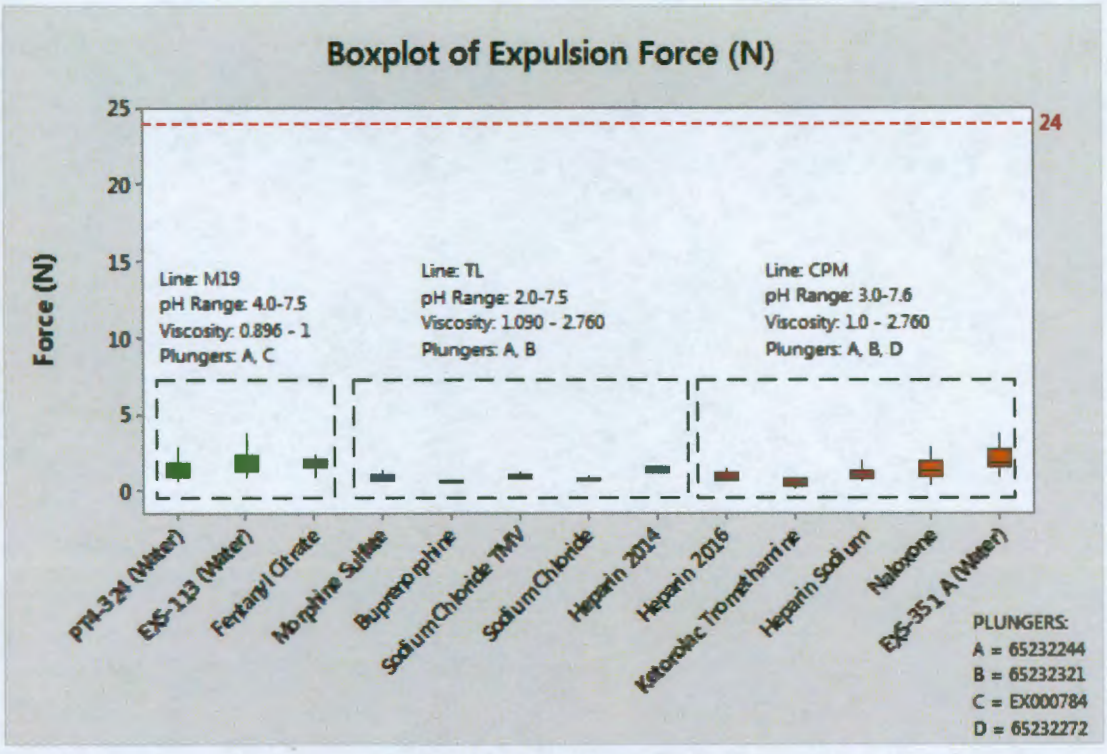


Figure 12. Expulsion Results Grouped by Filling Line

Carpuject Mini considered solution pH and viscosity for potential impact; however, upon review of the Carpuject Mini data it was determined that the pH and viscosity ranges in the portfolio do not impact the expulsion force, as described below. Figures 13 and 14 provide comparisons of expulsion force results within the same configurations at opposite ends of the pH and viscosity ranges. Ketorolac Tromethamine and Buprenorphine have identical elastomeric enclosures but represent the highest and lowest pH ranges, respectively. Heparin Sodium and Morphine Sulfate have identical elastomeric closures but represent the highest and lowest pH ranges and highest and lowest viscosities, respectively, for the elastomer type.

The data demonstrate that differences between expulsion forces tested with drug products having the highest and lowest pH are not statistically significant. Similarly, the data demonstrate that differences between expulsion forces tested with drug products having the highest and

lowest viscosities are not statistically significant. Therefore, Barracuda will not require bracketing of solution pH or viscosity for expulsion force testing.

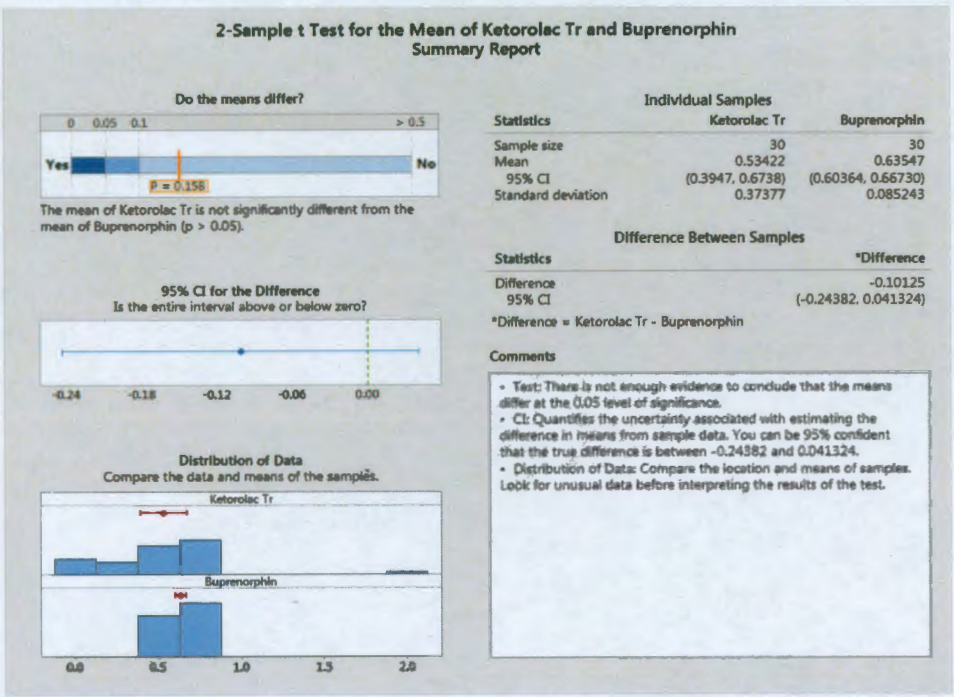


Figure 13. Two Sample t-Test between Ketorolac Tromethamine and Buprenorphine Expulsion Force

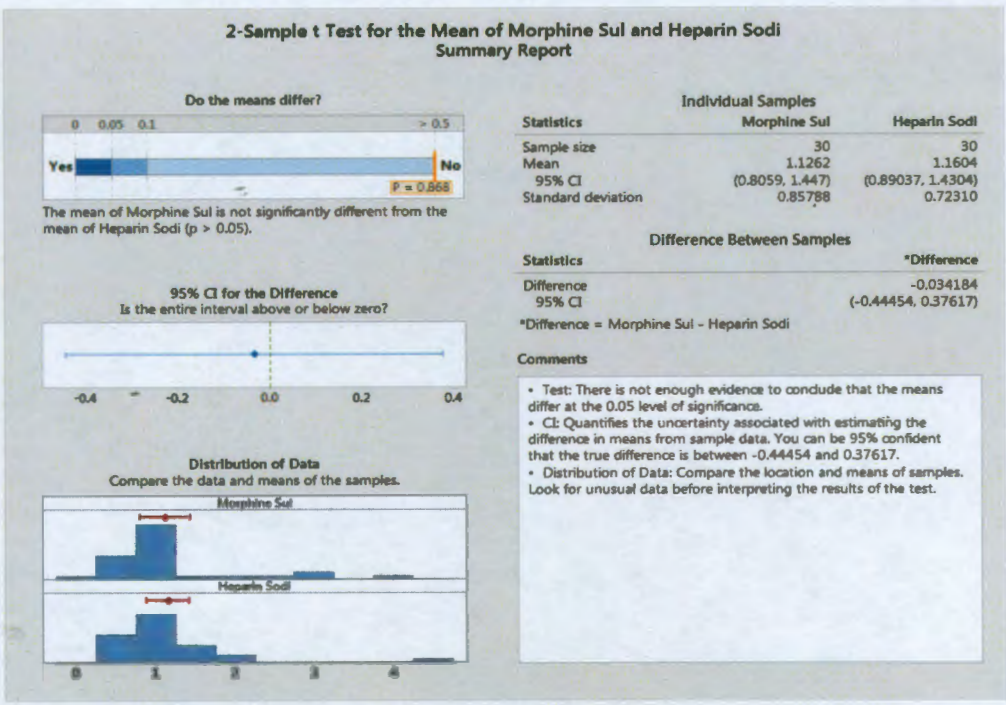


Figure 14. Two Sample t-Test between Morphine Sulfate and Heparin Sodium Expulsion Force

Fentanyl Citrate and Buprenorphine are out of scope based on the Barracuda 1 mL drug portfolio and thus only Morphine Sulfate, Ketorolac Tromethamine, Naloxone, and Heparin Sodium remain from the original Carpuject Mini bracketing. The differences in mean expulsion forces for Morphine Sulfate, Ketorolac Tromethamine, Naloxone, and Heparin Sodium are shown in Figure 15. Ketorolac is significantly lower than Ketorolac Tromethamine, Naloxone, and Heparin Sodium and would not represent the worst case. There are no statistical differences between Ketorolac Tromethamine, Naloxone, and Heparin Sodium; therefore, any of those configurations can be used in design verification.

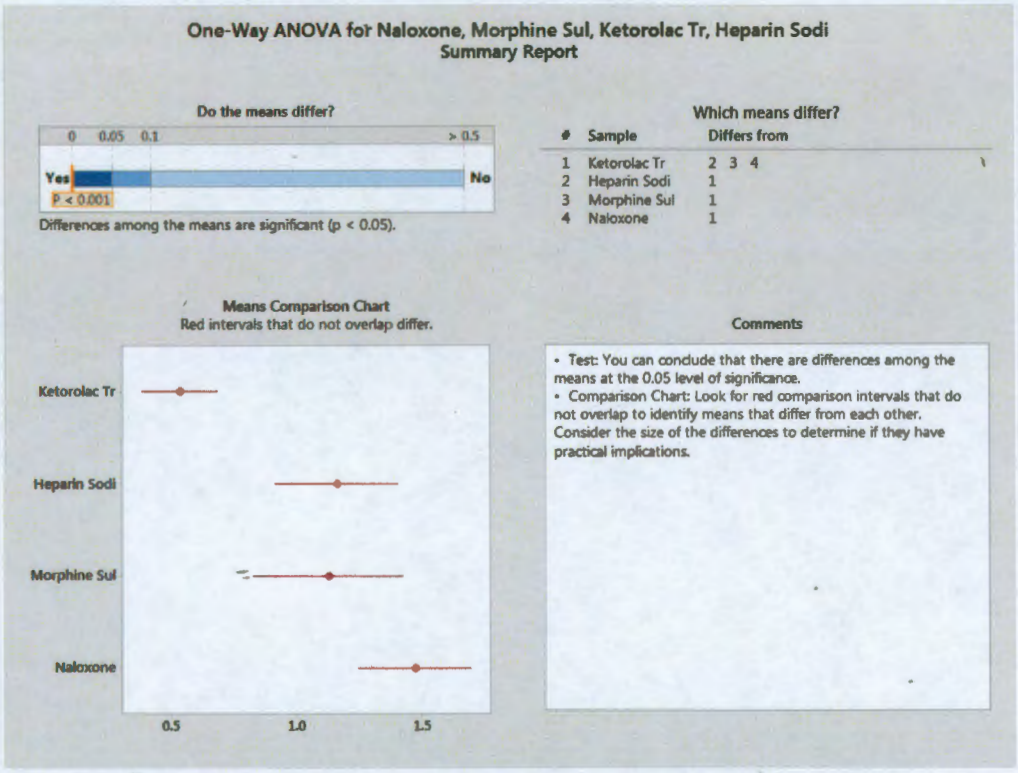


Figure 15. Analysis of the Difference in Means for Ketorolac Tromethamine, Heparin Sodium, Morphine Sulfate, or Naloxone.

Conclusion

The prefilled syringe is a complex system where the component characteristics often depend on the material of construction and processing conditions, which results in variability of the component attributes such as silicone oil level, drug property, and plunger formulation (Ng, Malone, Xiong, & Yi, 2013). The final assessment of drug attributes that will impact the device features are shown in Table 7, and the attributes which have changed from the original bracketing approach used for Carpuject Mini are identified with a bold border line. The final corner cases for each device function test are identified in Table 8.

Table 7

Final Assessment of Drug Attributes that Potentially Impact Device Features

Device Features	**Drug Attributes**					
	Solution pH	**Viscosity**	**Elastomer Formulation**	**Plunger Height**[1]	**8-I Seal Thickness**	**Filling Line**
Break Loose Force	No Impact[2]	No Impact	Potential Impact	Potential Impact	No Impact	Potential Impact
Expulsion Force	No Impact[2]	No Impact[2]	Potential Impact	Potential Impact	No Impact	No Impact[2]

[1] Note all plungers have the same outer diameter, thus only plunger height was considered as a drug attribute that required a bracketing approach.

[2] Attributes changed from initial assessment provided in Table 2 due to data analysis provided in this document.

Table 8

Corner Case Summary

Device Feature	**Design Input**	**Corner Case**
Break Loose Force	DI-BAR-15	Design Verification testing shall be performed using the elastomeric closure of the Heparin Sodium configuration and manufactured on the M19 filling line. Sample may be water-filled as there is no impact from drug solution attribute.

Expulsion Force	DI-BAR-17	Design Verification testing shall be performed using elastomeric closures from any of the following configurations: Heparin Sodium, Naloxone, or Morphine Sulfate. Sample may be water-filled as there is no impact from drug solution attribute.

All other testing for a manual push syringe system may be performed using water-filled cartridge units because the drug attributes do not impact the functionality.

Summary

In this paper a test method of break loose and expulsion forces was addressed, which is part of the syringe product life cycle development. The general corner case determination procedure was analyzed to optimize the workload and to verify the worst case of a product family. Statistic methodologies and tools learned from courses in the Master of Science program were employed to support the data analysis. Based on the tolerance analysis and two sample t-test results, a corner case of Barracuda 1mL syringe was determined with supportive data.

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