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S.1. General Information

S.1.1. Nomenclature

Chemical Names

IUPAC: (3*R*,4*R*,5*S*)-1-{[(3*S*,4*R*)-1-*tert*-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-4-hydroxy-3,5-dimethyl-4-phenylpiperidine hydrochloride

CAS Registry Name: (3 α ,4 α ,5 α)-1-[[[(3*S*,4*R*)-4-(2,4-difluorophenyl)-1-(1,1-dimethylethyl)-3-pyrrolidinyl]carbonyl]-3,5-dimethyl-4-phenyl-4-piperidinol monohydrochloride

Internal Laboratory Identification Numbers

PF-00446687-01

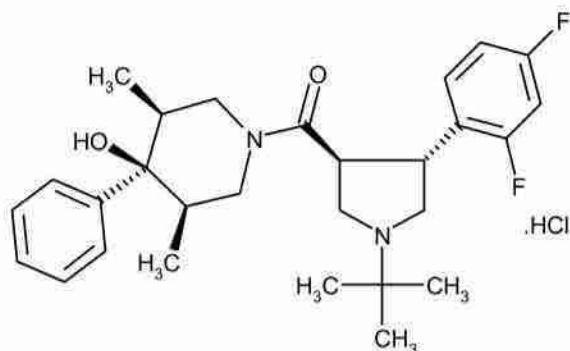
CAS Registry Number

862281-92-3

S.1.2. Structure

Chemical Structure

Figure S.1.2-1. PF-00446687-01 Structure



Molecular Formula

$C_{28}H_{37}ClF_2N_2O_2$

Molecular Weight

507.07 Da

S.1.3. General Properties

Table S.1.3-1. Drug Substance General Properties

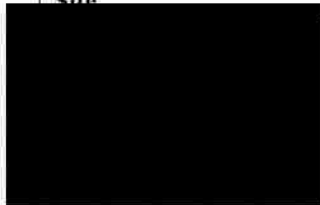
Property	Description/Result
Description	White solid of uniform appearance, essentially free from visible foreign matter
pKa	9.2
Apparent 1-Octanol/Water Partition Coefficient	Log D _{7.4} = 2.8
Solubility	6.3 mg/mL, in 0.01 M HCl
Melting Point	285.0°C
Powder X-Ray Diffraction	Confirms material is highly crystalline.
Polymorphism	
Hygroscopicity	Non-hygroscopic. Moisture uptake of 0.15%w/w at 90%RH.

S.2. Manufacturer

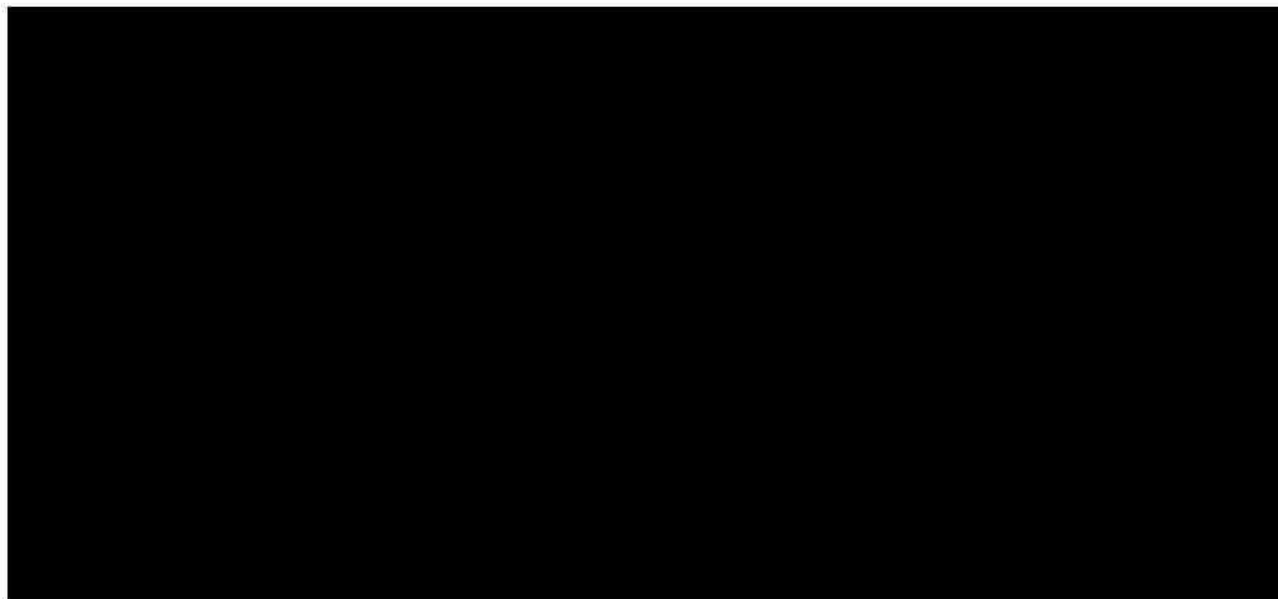
S.2.1. Manufacturer

The address of the manufacturing, release testing and release site for PF-00446687-01 is provided in Table S.2.1-1.

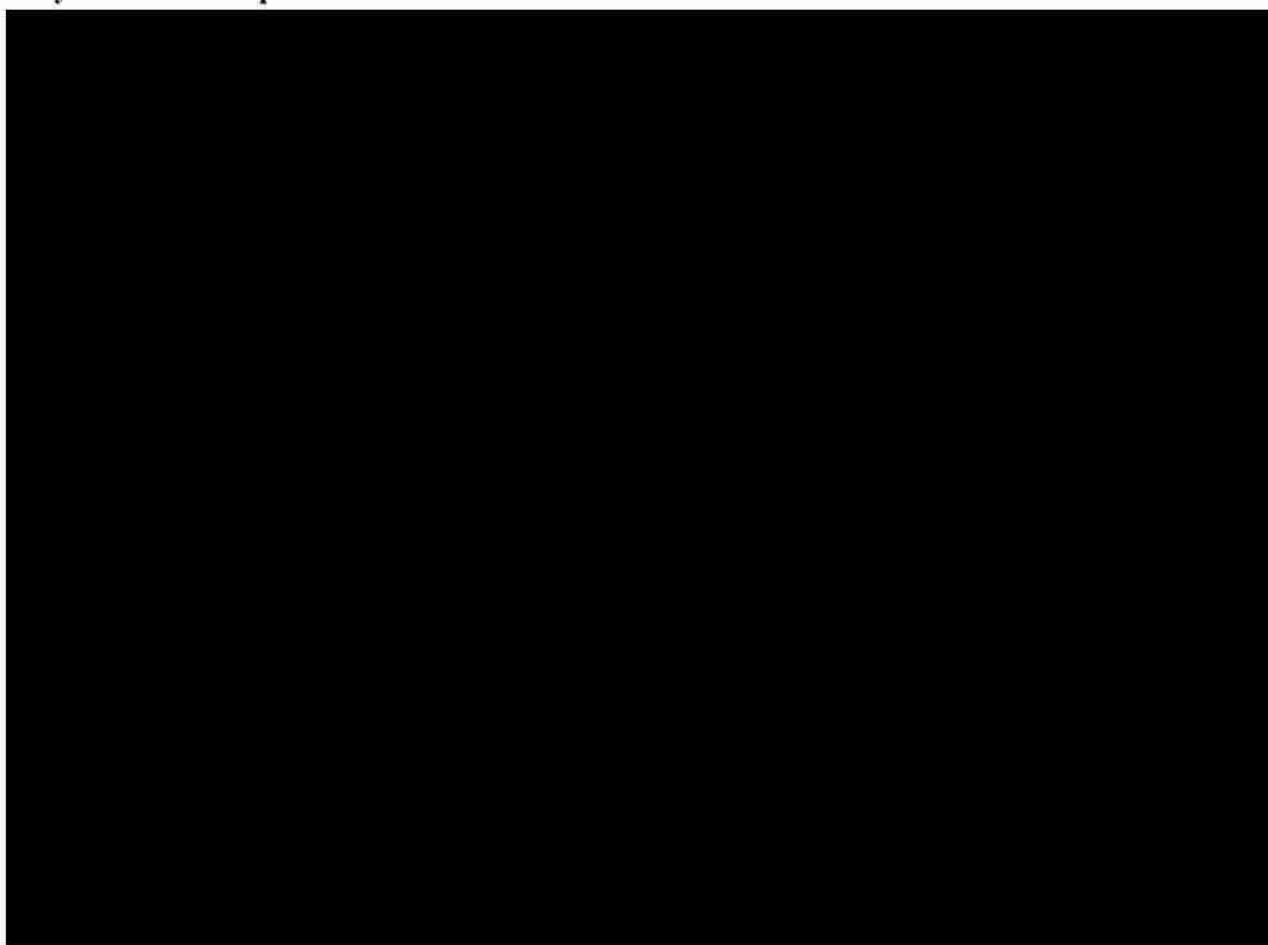
Table S.2.1-1. Site and Responsibilities for Manufacture, Release Testing and Release of PF-00446687-01

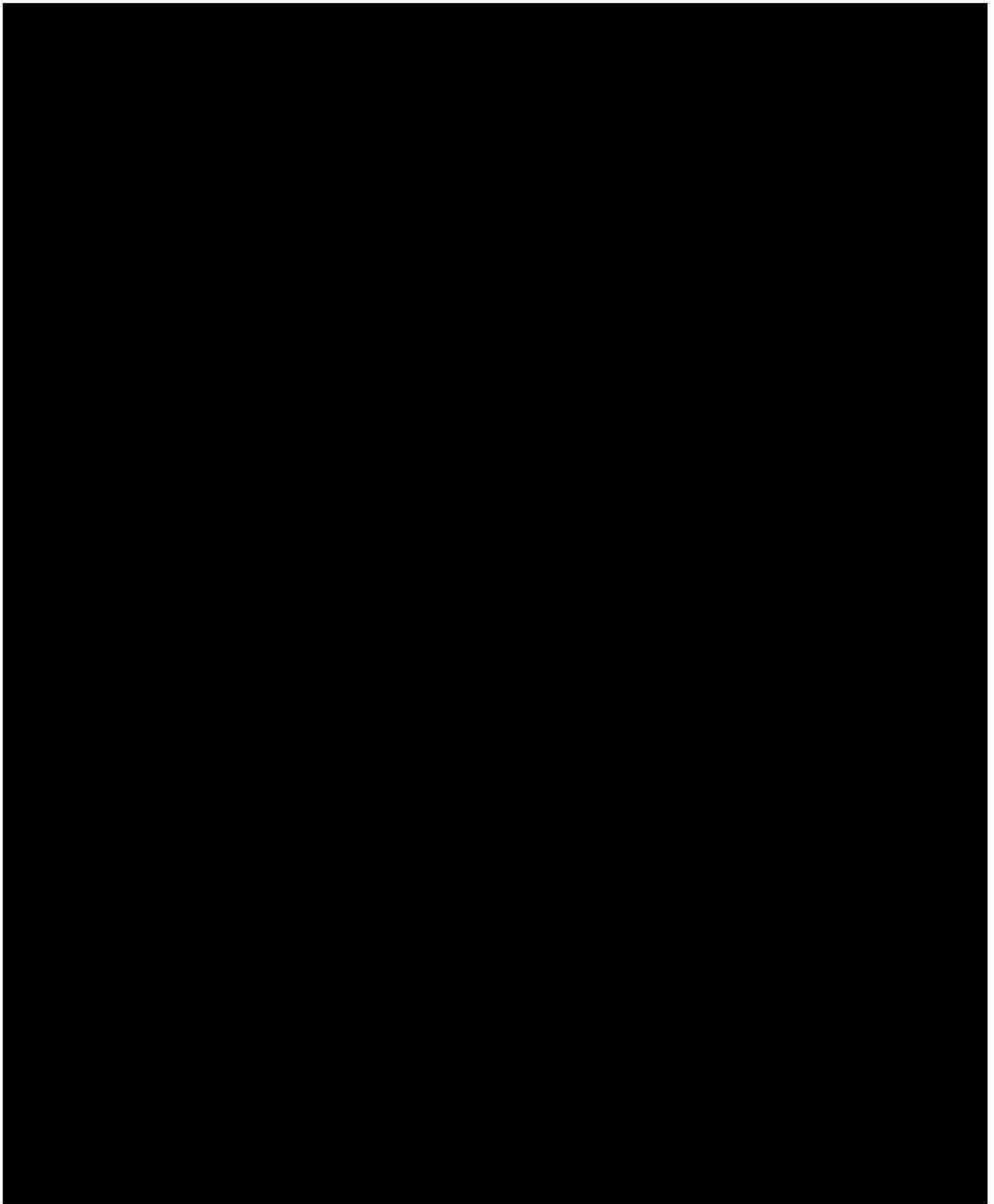
Site	Responsibility
	Manufacture, release testing and release

S.2.2. Description of Manufacturing Process and Process Controls

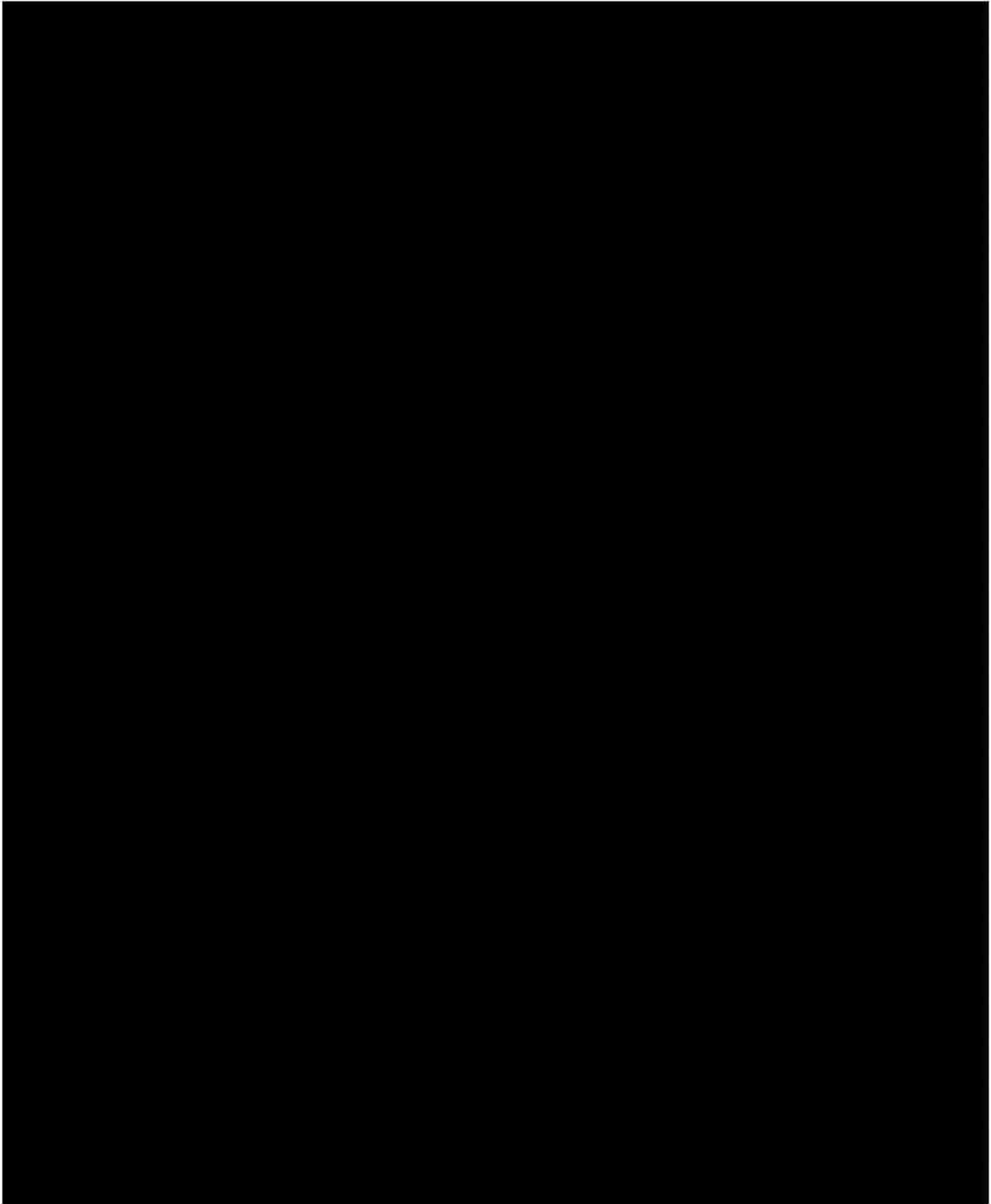


Synthetic Description





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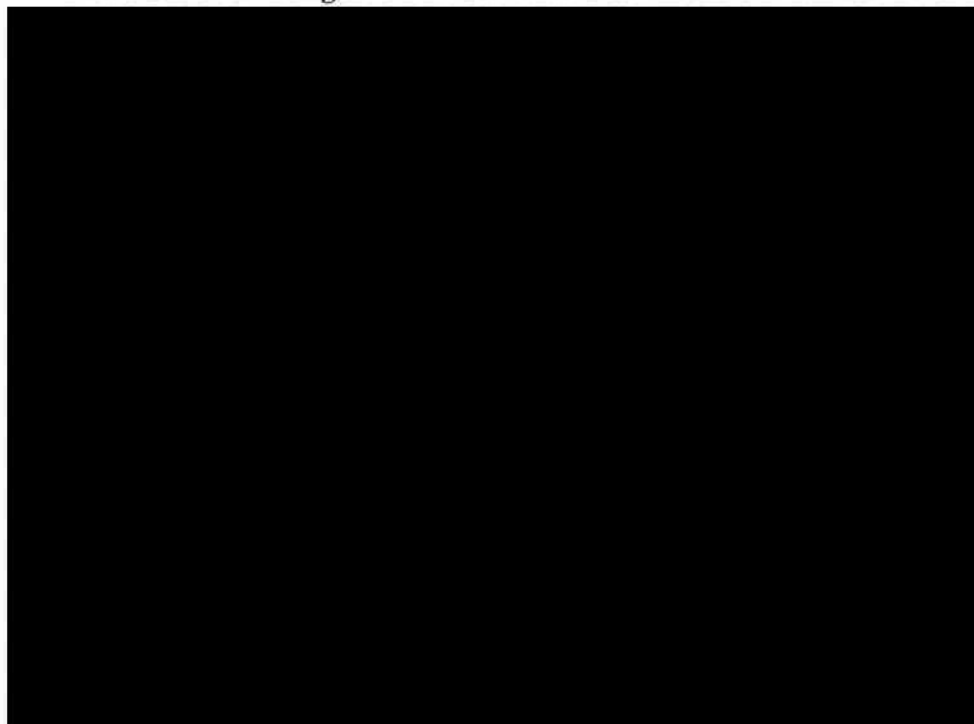
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S.2.3. Control of Materials

Reagents, Solvents, and Catalysts

At this stage in the development of PF-00446687-01, emphasis has been placed on the control of the key raw materials and intermediates that make a significant contribution to the structure of the PF-00446687-01 molecule to ensure the quality of the final product. All purchased materials, including key structural fragments, reagents, solvents and processing aids, used in the manufacture of PF-00446687-01 are obtained from reputable suppliers to standards judged to be acceptable for the manufacture of a new drug substance.

Table S.2.3-1. Reagents and Solvents Used in the Manufacture of PF-00446687-01



S.2.4. Control of Critical Steps and Intermediates

There are no critical steps identified in the manufacture of PF-00446687-01 drug substance.

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S.2.5. Process Validation and/or Evaluation

This section is not applicable at this stage of development. There is no aseptic processing or sterilization for PF-00446687-01.

S.2.6. Manufacturing Process Development

This section is not applicable at this stage of development.

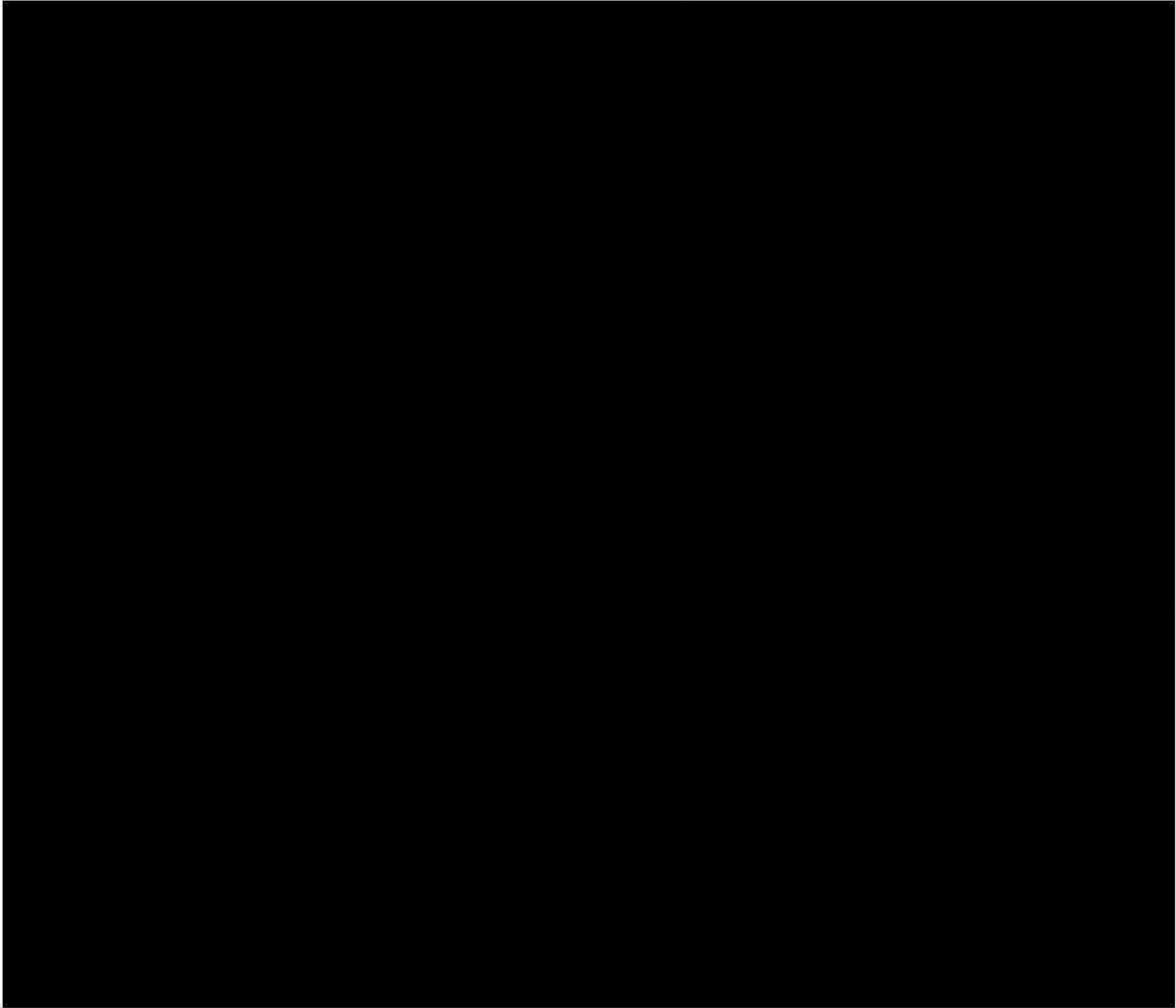
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S.3. Characterisation

S.3.1. Elucidation of Structure and Other Characteristics

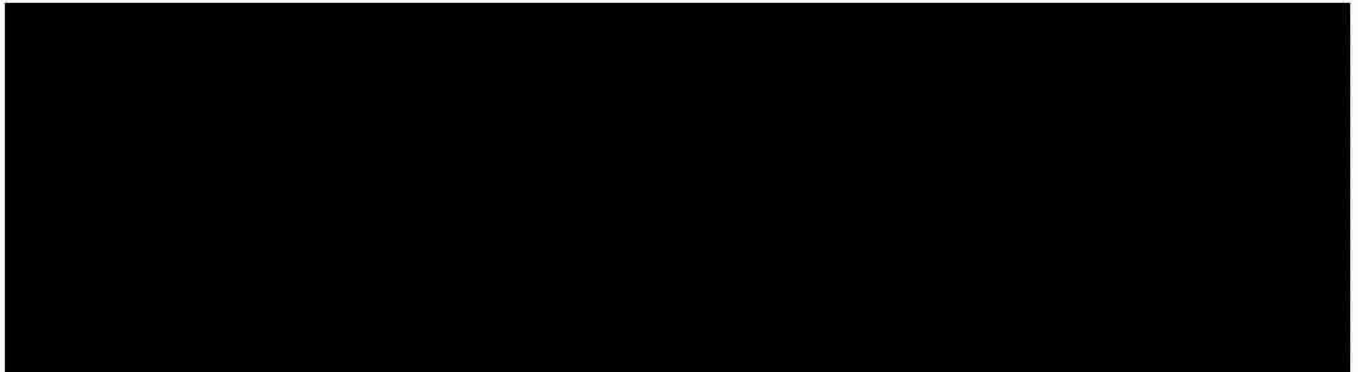
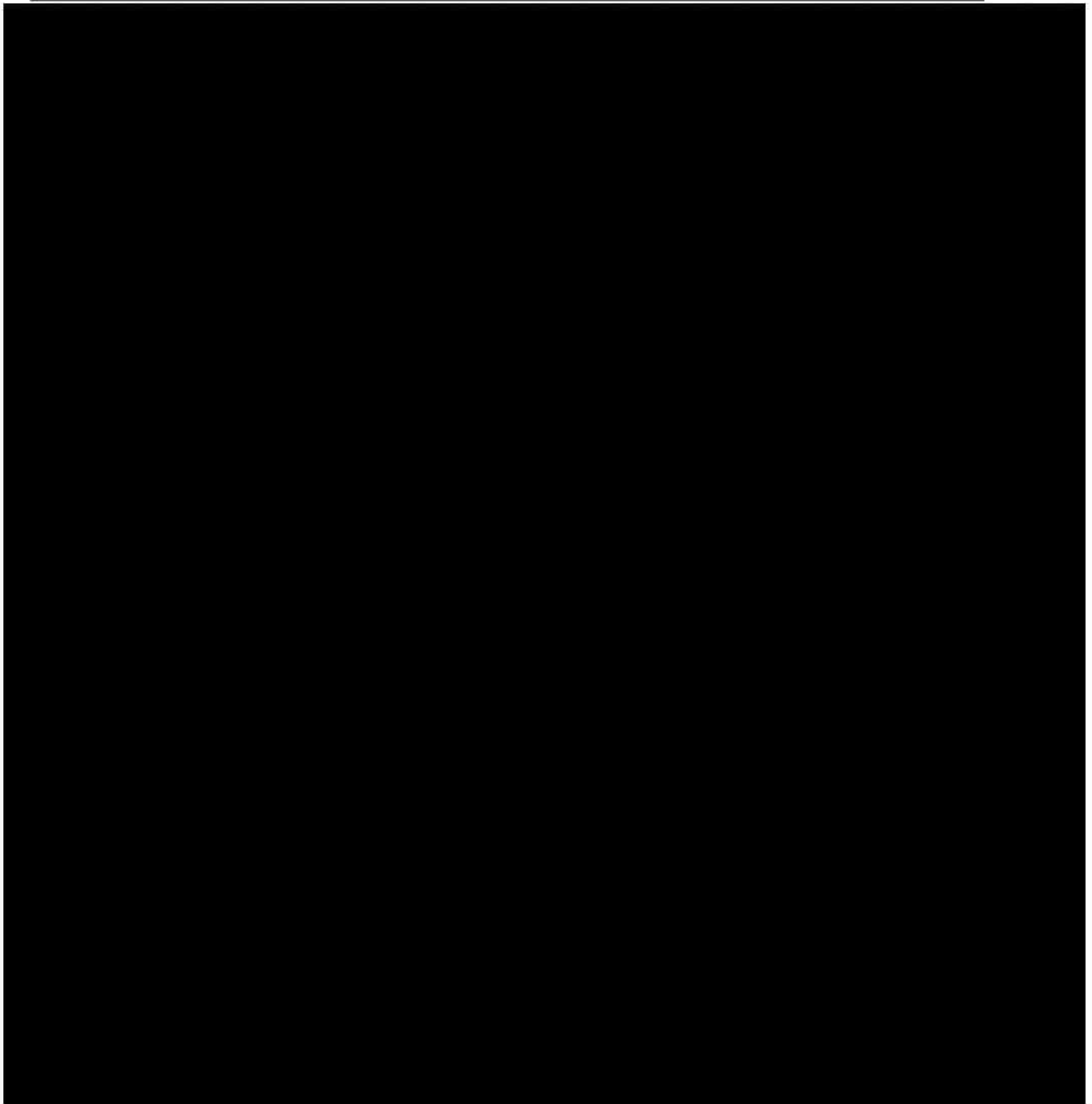
Introduction

The established structure of PF-00446687-01 is consistent with the method of synthesis and all micro-analytical and spectroscopic data obtained from the analysis of PF-00446687-01. The structural formula, molecular formula, and molecular weight are presented in [Section S.1.2 Structure \(PF-00446687-01\)](#). Details of the analyses to elucidate the structure follow.

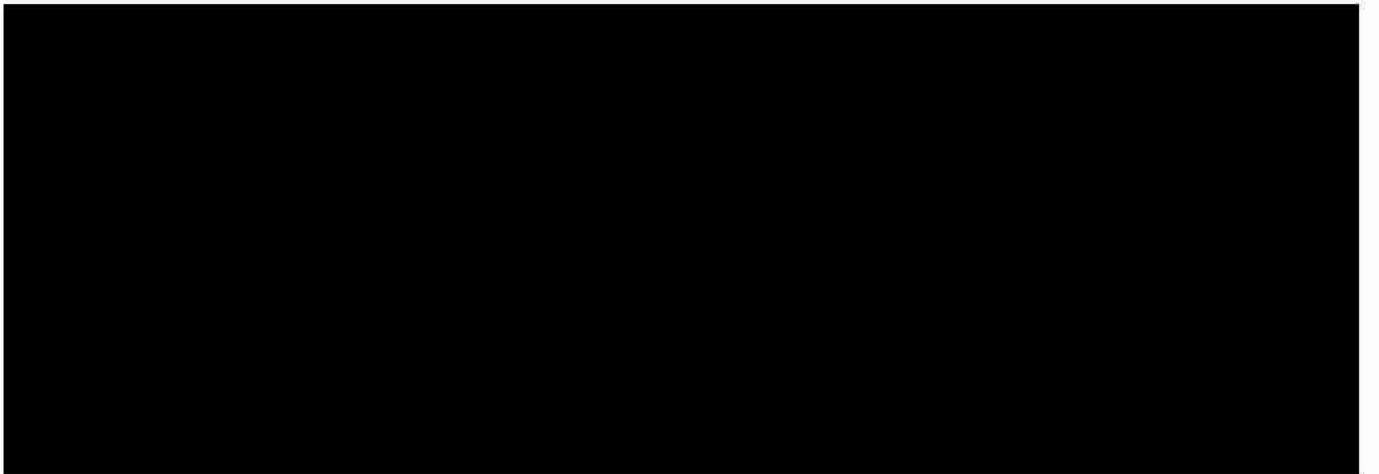
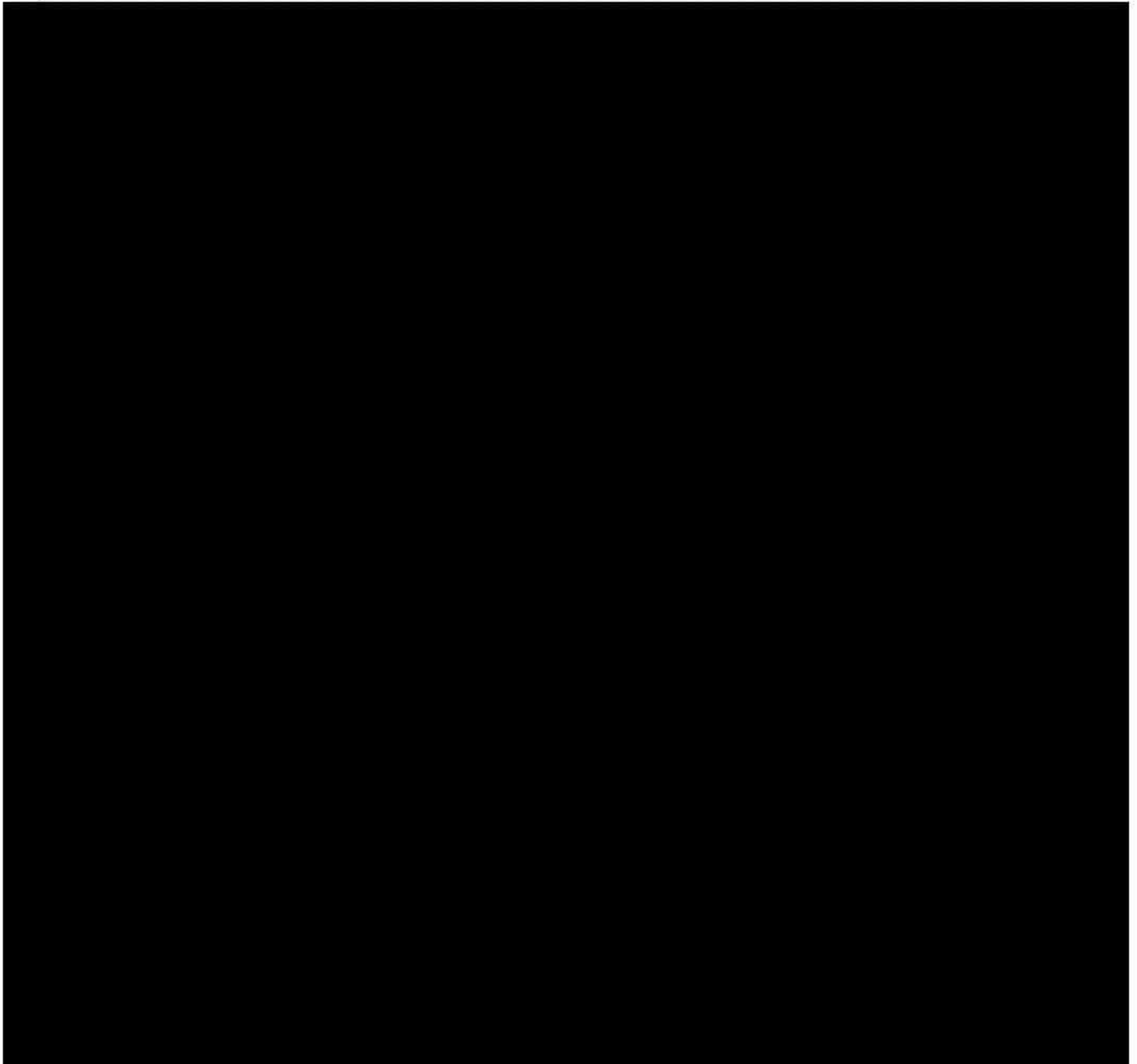


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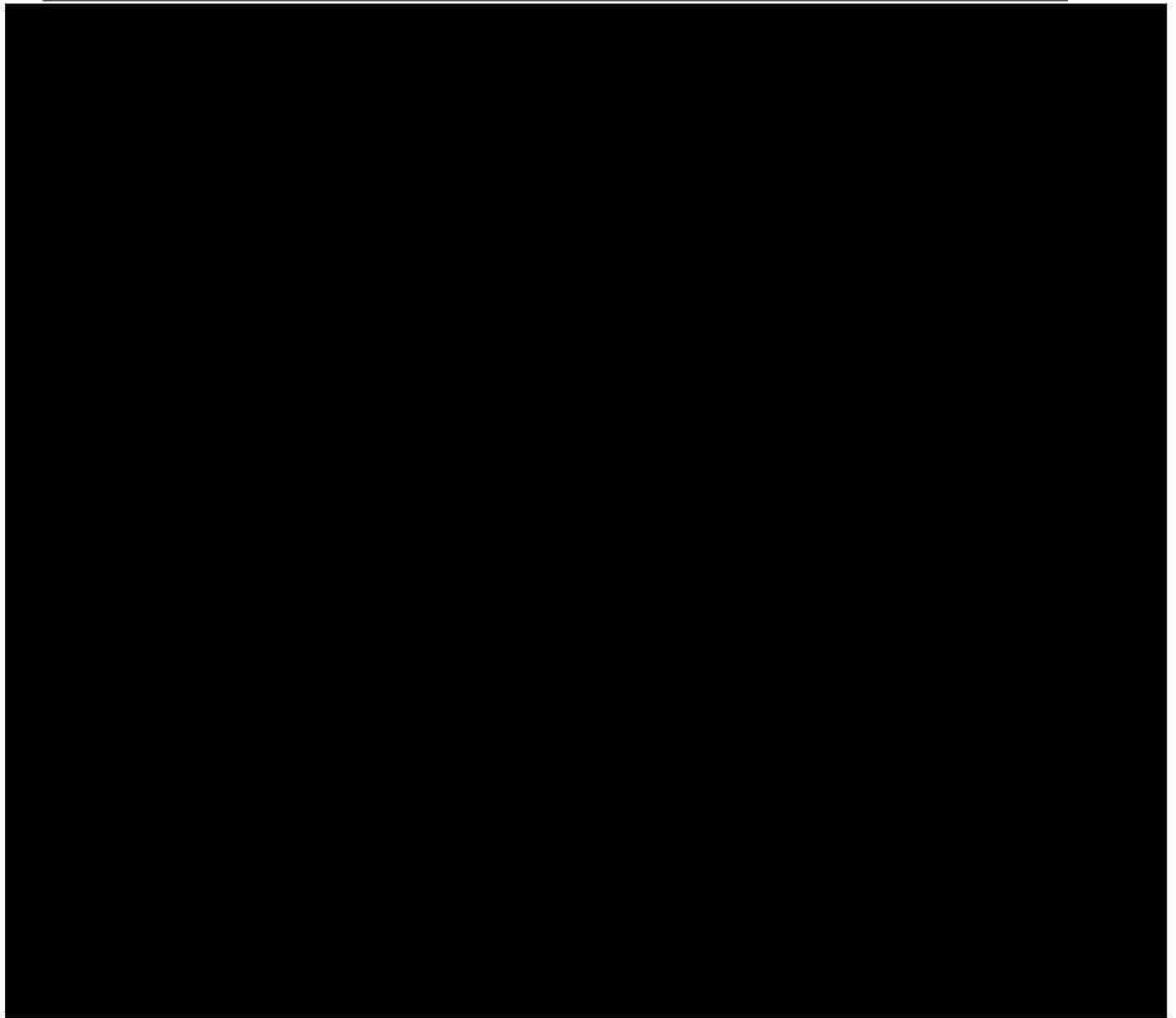
S.3.1 Elucidation of Structure and Other Characteristics



S.3.1 Elucidation of Structure and Other Characteristics



S.3.1 Elucidation of Structure and Other Characteristics

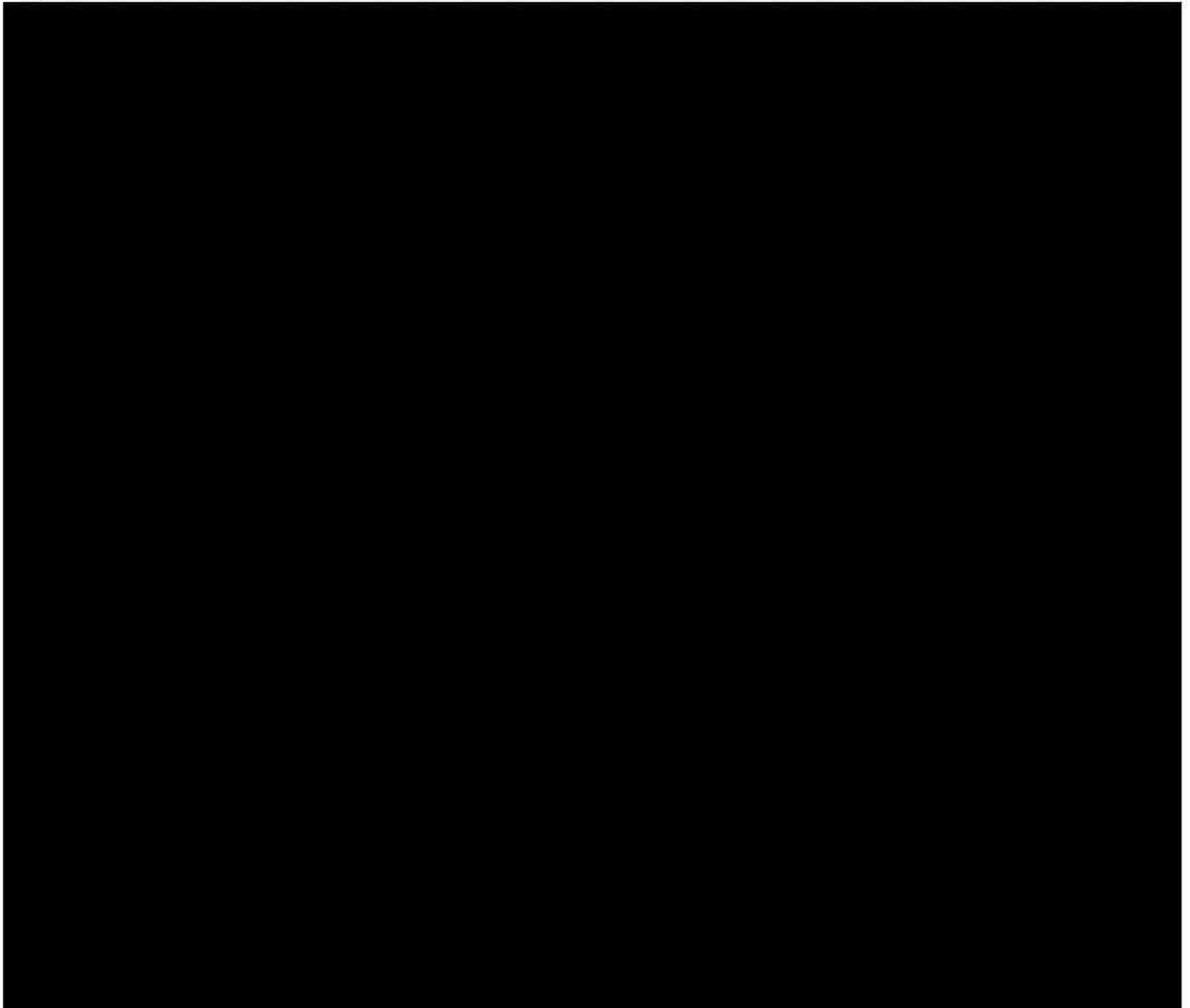


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S.3.1 Elucidation of Structure and Other Characteristics

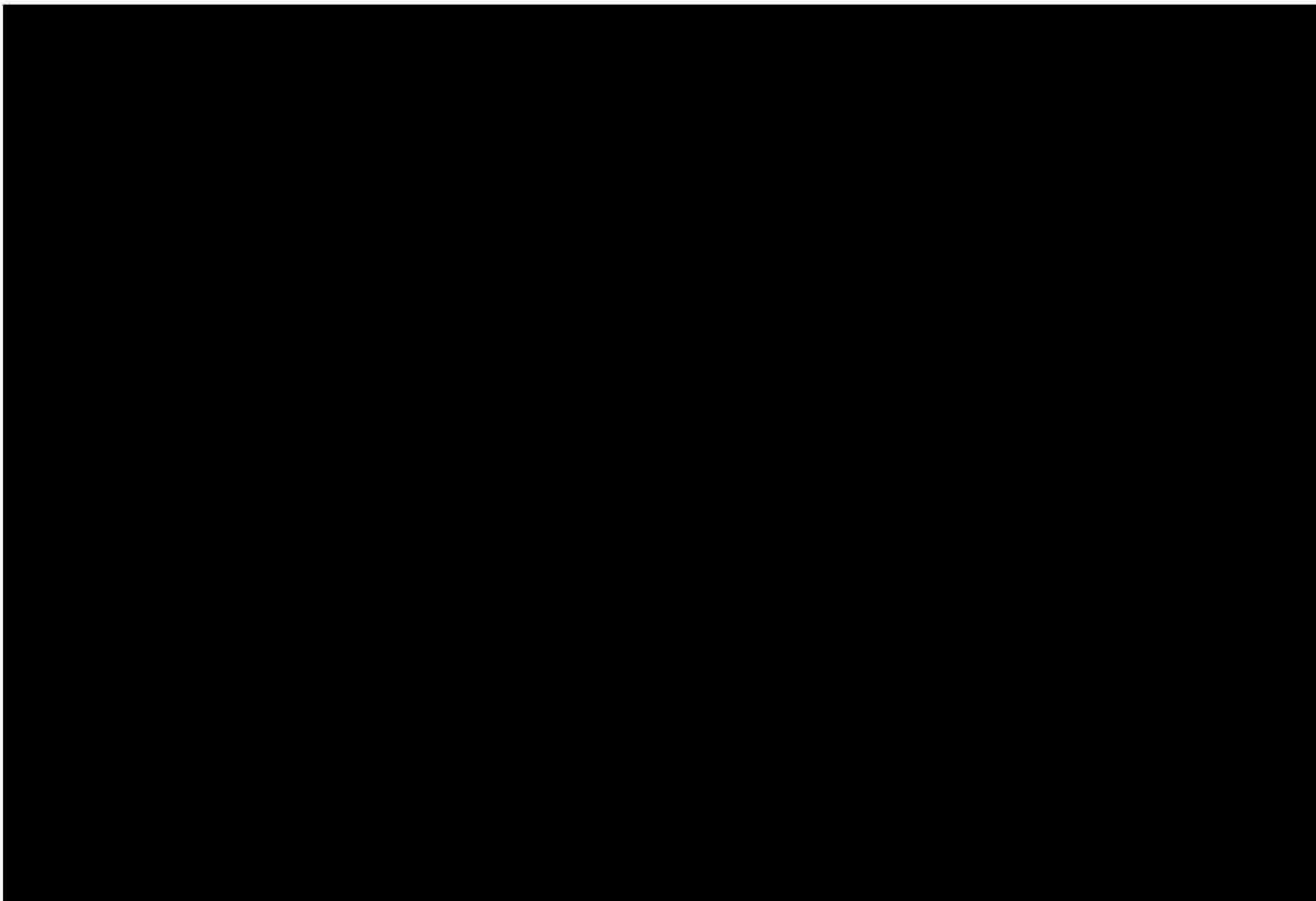
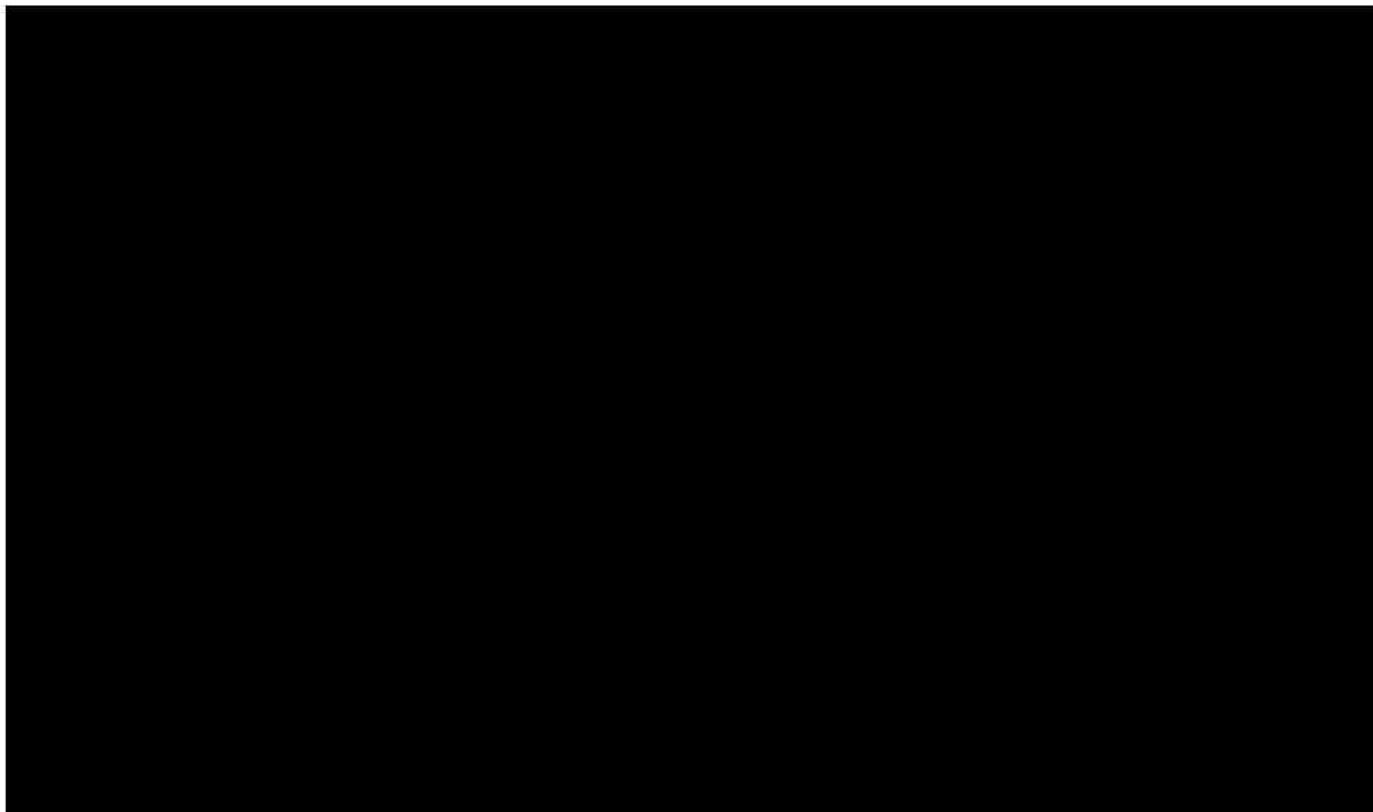
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S.3.1 Elucidation of Structure and Other Characteristics

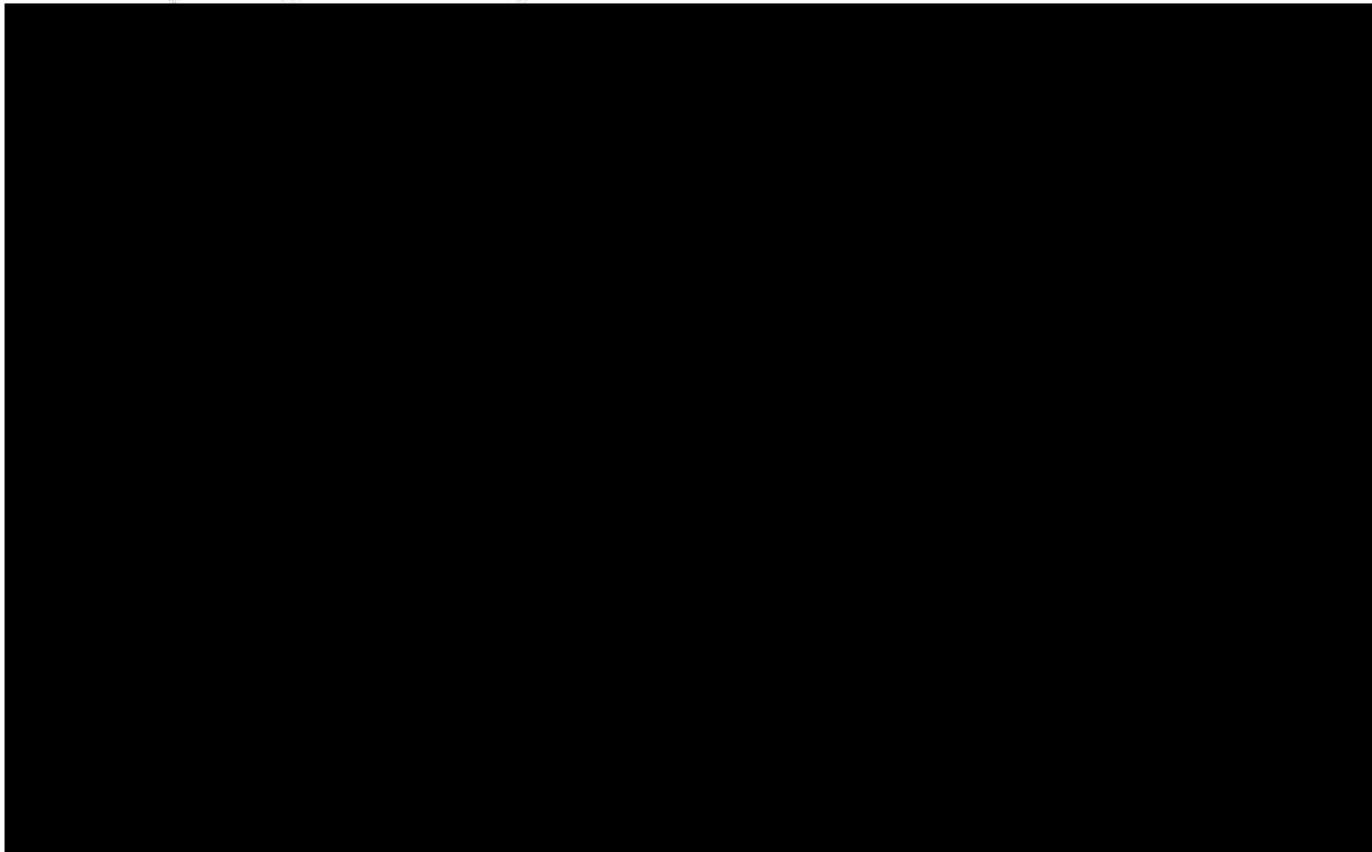


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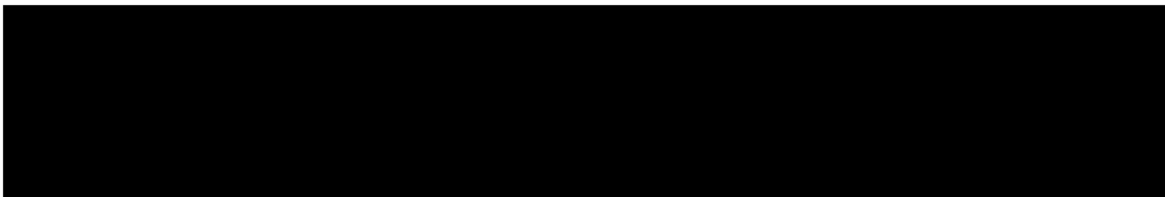
S.3.1 Elucidation of Structure and Other Characteristics



S.3.2. Impurities (PF-00446687-01)



Inorganic Impurities



Heavy Metals



Residual Solvents



Table S.3.2-2. Solvents Used in all Stages of the Synthesis of PF-00446687-01



Water

Water content is controlled in the specification for PF-00446687-01 drug substance.

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S.4. Control of Drug Substance

S.4.1. Specification

The specification for PF-00446687-01 are in Table S.4.1-1.

Table S.4.1-1. PF-00446687-01 Specifications

Test Name	Test Method	Pfizer Method Number	Acceptance Criteria
Description			
Appearance	Visual		
Solution Clarity	Visual		
Identification			
Identity	FT-IR		
Identity	Chiral HPLC		
Assay			
PF-00446687	HPLC		
HCl counter-ion	Potentiometric Titration		
Impurities			
Residue on Ignition	Sulfated Ash		
Heavy Metals	USP <231>		
Water	Karl Fischer		
Individual Unspecified Impurities	HPLC and Chiral HPLC		
Total Related Impurities	HPLC and Chiral HPLC		
	GC		
Residual Solvents			
	GC		
	GC		

NMT = Not more than

S.4.2. Analytical Procedures

Appearance (RA-1327)

Visual inspection of the sample is performed.

Solution Clarity (F 6.0)

[REDACTED]

Fourier Transform Infrared Spectroscopy

[REDACTED]

Residue on Ignition – Sulphated Ash

[REDACTED]

Heavy Metals

[REDACTED]

Water Content by Coulometric Karl Fischer

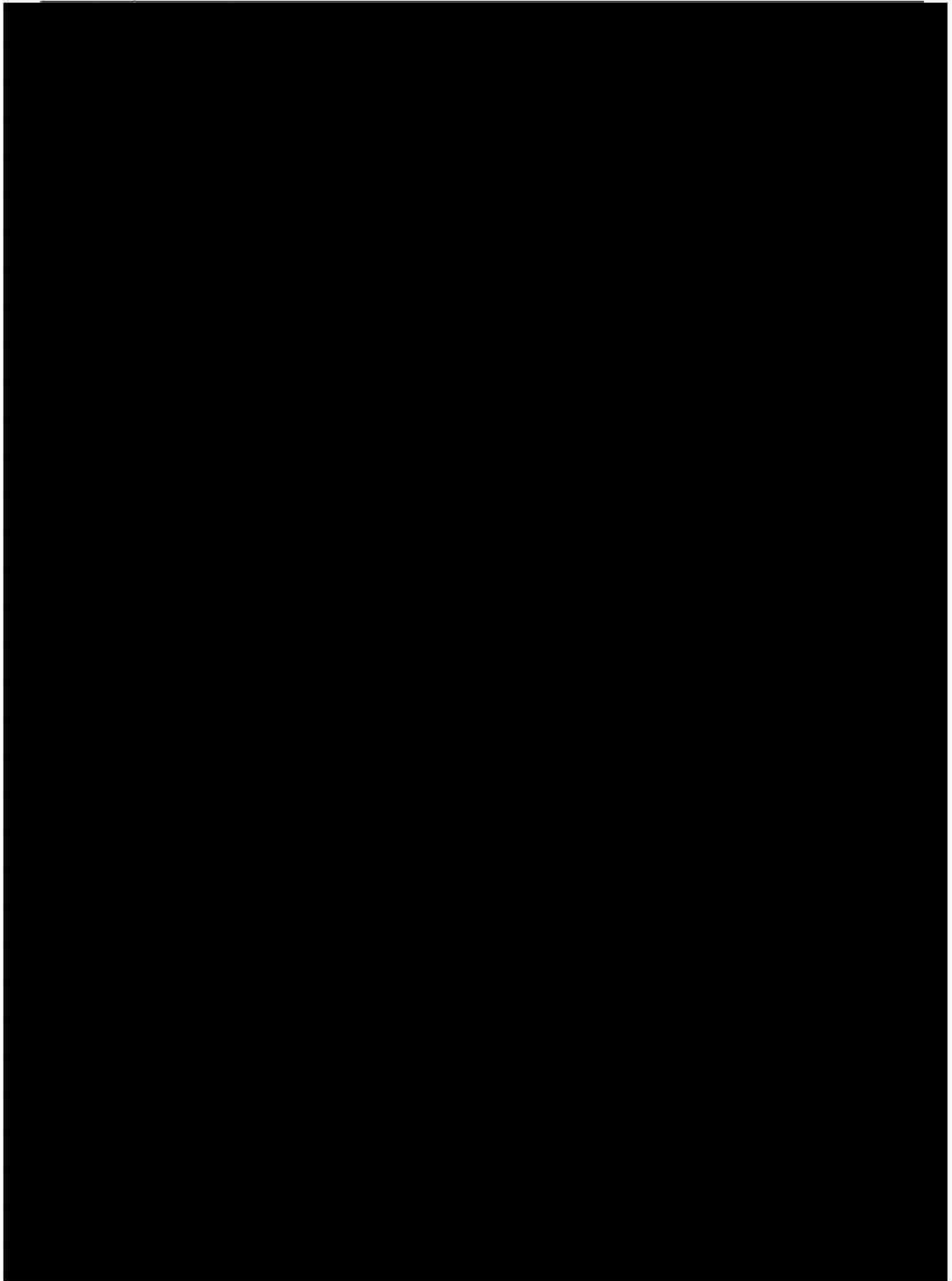
[REDACTED]

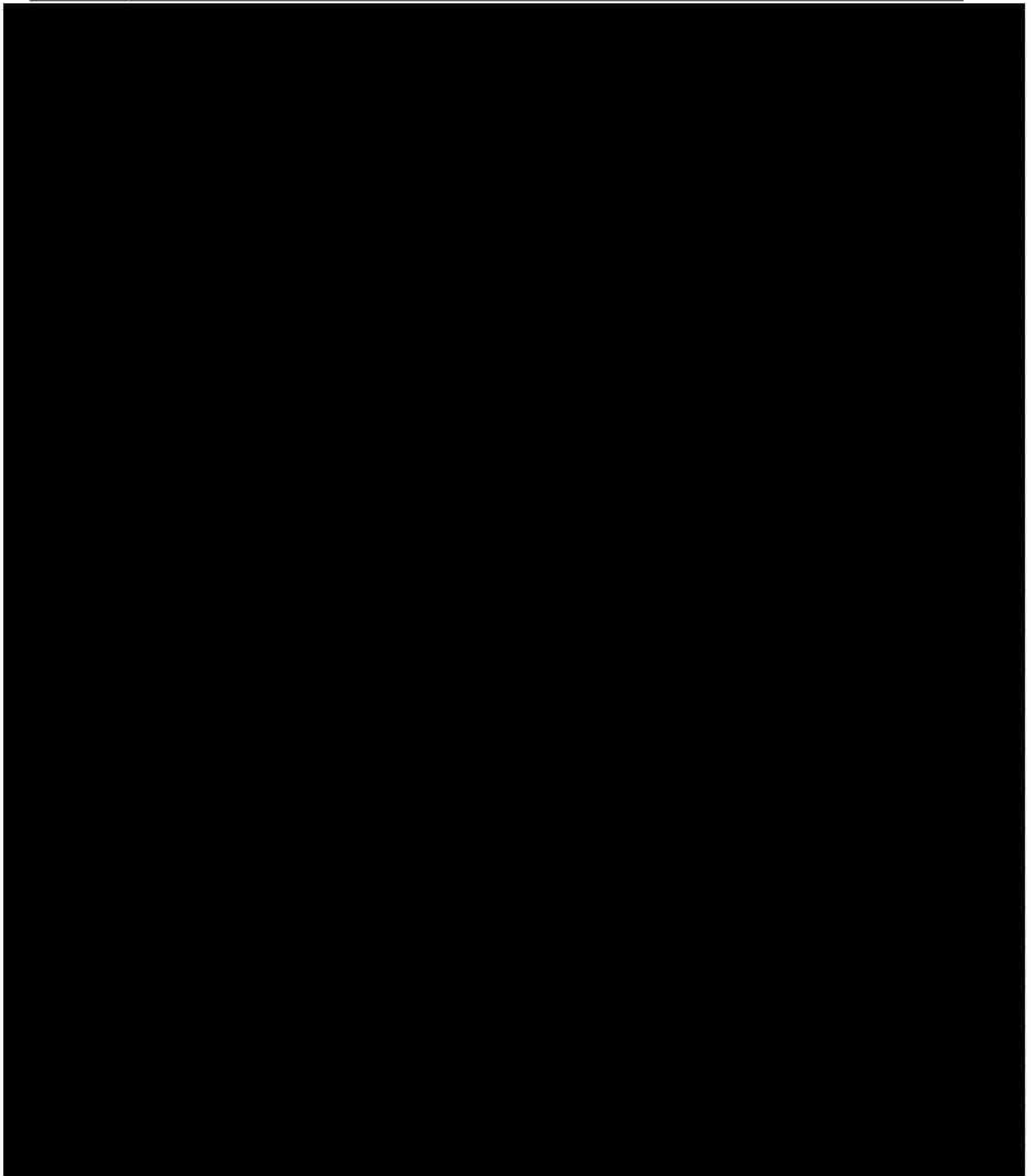
HCl Counter-Ion Content by Potentiometric Titration

[REDACTED]

Assay and Achiral Purity by HPLC

[REDACTED]

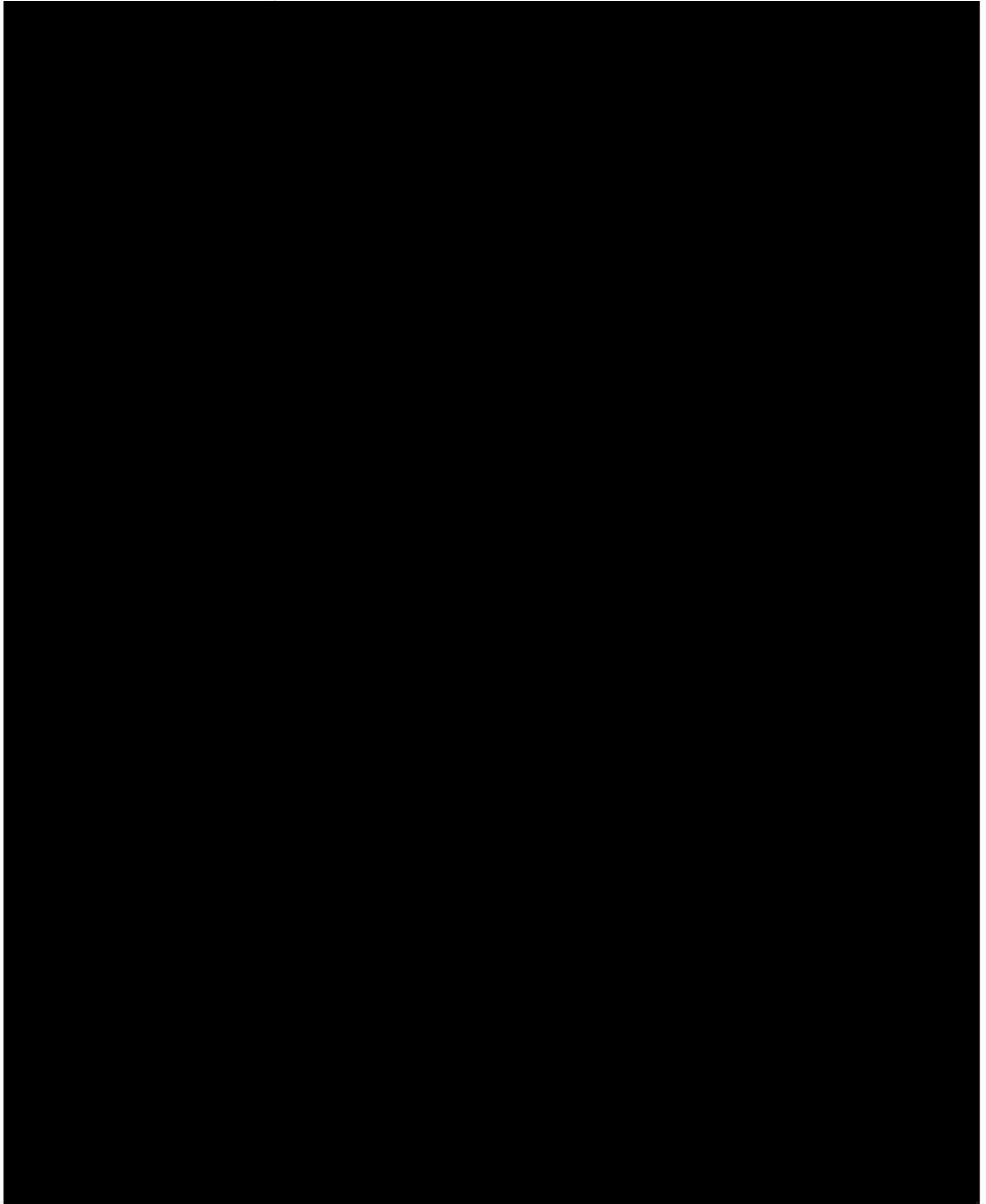


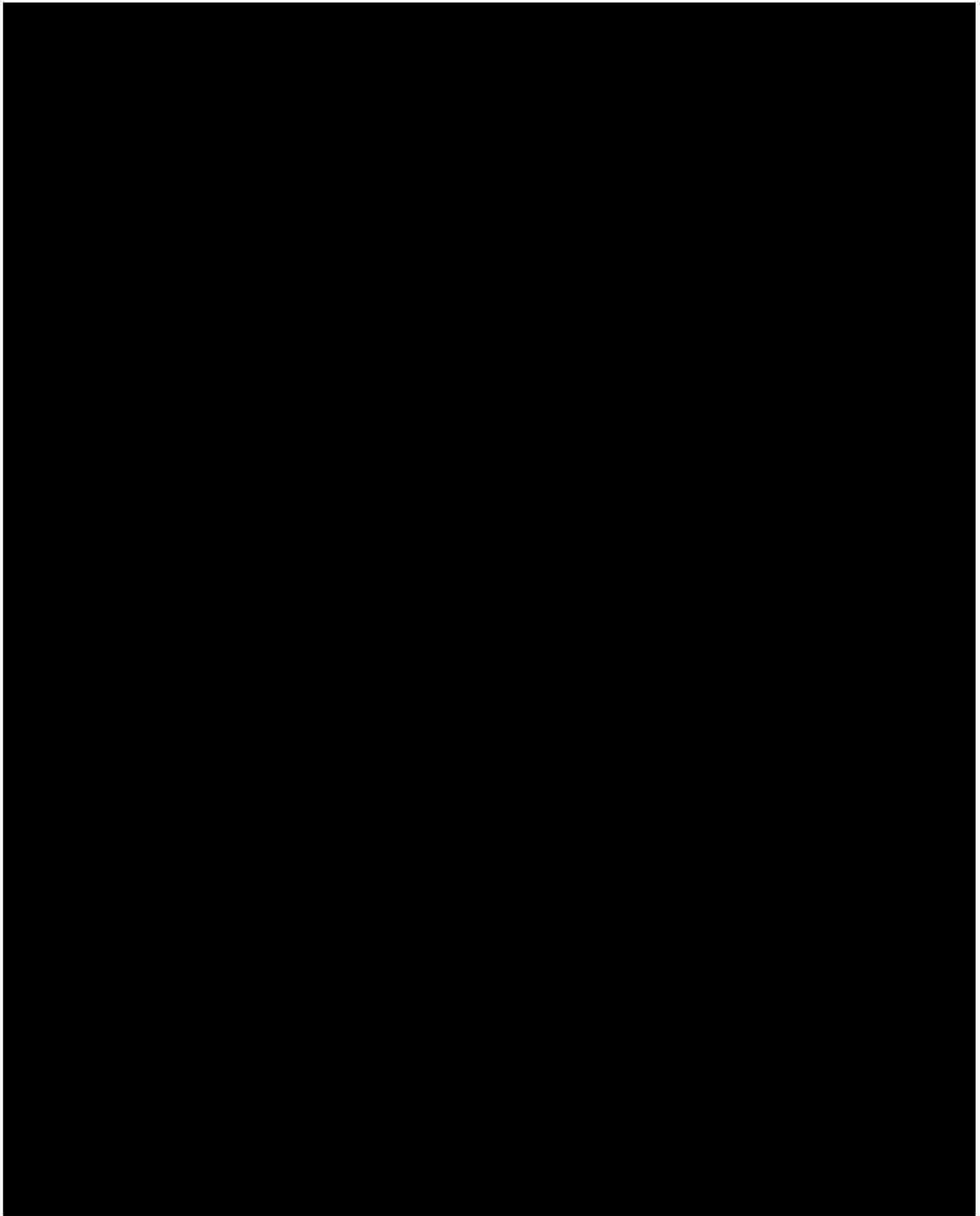




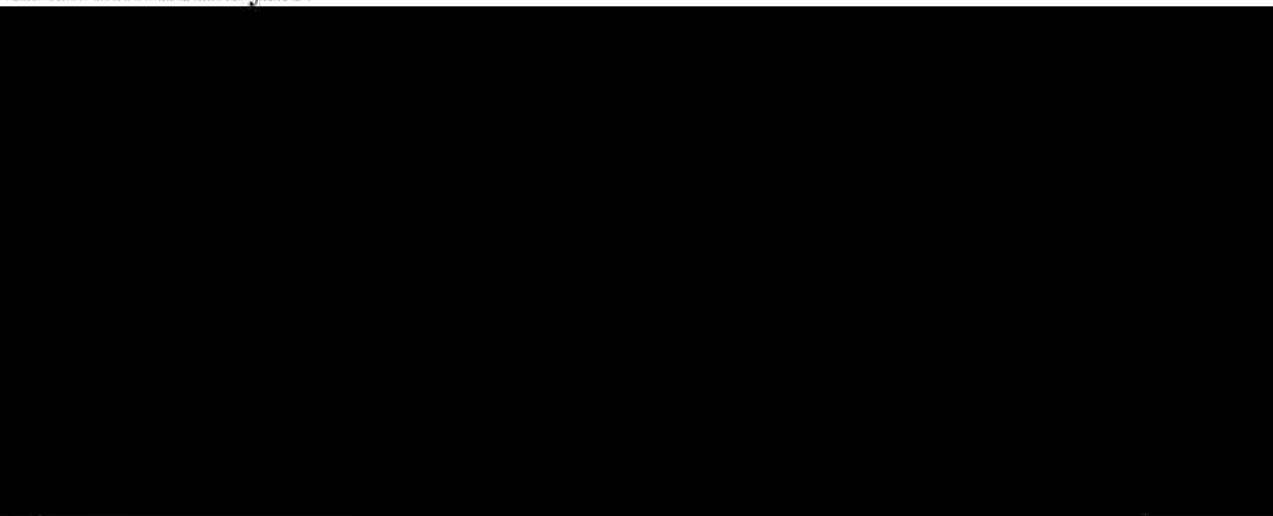
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S.4.3. Validation of Analytical Procedures





S.4.4. Batch Analyses



Appearance
Solution Clarity
Identification
Identity (FT-IR)
Identity (Chiral HPLC)
Assay
PF-00446687 (HPLC)
HCl counter-ion
Impurities
Residue on Ignition
Heavy Metals
Water
Individual Unspecified Impurities
Total Related Impurities
Residual Solvents

NMT = Not more than

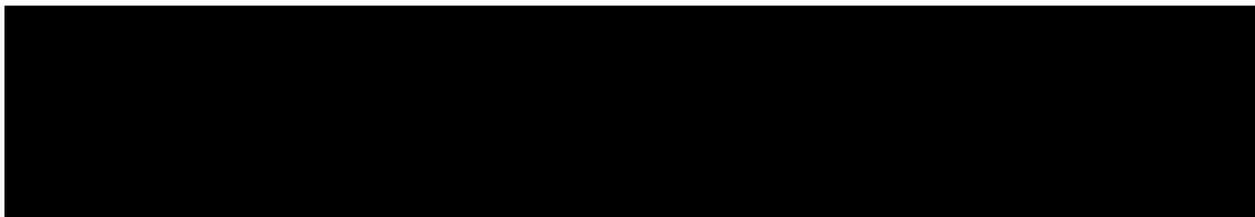
S.4.5. Justification of Specification

The drug substance specification for PF-00446687-01 has been established to ensure the safety and consistency of the product.

At this stage of development specification tests and acceptance criteria are based on safety and suitability considerations. Appearance, identity, chiral configuration and purity, assay and achiral purity, hydrochloride content, residual solvents, water, heavy metals,

[REDACTED]
[REDACTED] and residue on ignition are all controlled to limits which have been assessed as safe and suitable for this stage of the product development.

S.5. Reference Standards or Materials



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S.6. Container Closure System**Description of Container Closure System**

PF-00446687-01 is stored in two sealed low-density polyethylene bags inside a high-density polyethylene (HDPE) container.

S.7. Stability

S.7.1. Stability Summary and Conclusions

General

PF-00446687-01, Batch [REDACTED] is currently undergoing a formal stability program in accordance with the stability protocol detailed in Table S.7.1-1.

Table S.7.1-1. Stability Protocol Applied to PF-00446687-01 [REDACTED]

Conditions	Initial	24hr/6d	2 wks	6 wks	3 mths	6 mths	12 mths	18 mths	24 mths
Photostability ⁽¹⁾	X	X							
5°C	X		X						
25°C/60%RH	X		X	X	X	Y	Y	X	Y
40°C/75%RH	X			X	X	Y			
50°C	X		X						

⁽¹⁾ Photostability parameters: 200 Wm²/1.2 10⁶ Lux

X indicates the following tests: Appearance, PXRD, DSC, achiral assay, impurities by HPLC, and water.

Y indicates that chiral HPLC analysis in addition to the above tests will be performed to ensure chiral purity

Container Closure System

Thermal stability samples of drug substance, PF-00446687-01, Batch [REDACTED] were packaged in two low-density polyethylene bags within a high-density polyethylene container to simulate bulk storage conditions. Photostability samples were stored in a quartz glass petri dish with a quartz lid.

Summary and Conclusion

At the time of submission, no formal stability data were available and PF-00446687-01, Batch [REDACTED] is currently being stored between 2°C and 8°C as a precaution prior to assessing stability data.

PF-00446687-01
S.7.3 Stability Data

S.7.3. Stability Data

Analytical Methods

[REDACTED]

Powder X-Ray Diffraction, PXRD

[REDACTED]

Differential Scanning Calorimetry, DSC

[REDACTED]

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P.1. Description and Composition of the Drug Product**Table P.1-1. Composition of Extemporaneously Prepared PF-00446687-01 Oral Solution**

Name of Ingredients	Reference to Standards	Function
PF-00446687-01	Pfizer	Active Pharmaceutical Ingredient
0.1 M Hydrochloric Acid ^a	Pfizer	Diluent
Water for Irrigation	Ph. Eur.	Diluent

^a The 0.1 M hydrochloric acid solution manufactured by Pfizer is used with the Water for Irrigation (Ph. Eur.) to extemporaneously prepare the final 0.01 M hydrochloric acid diluent.

The solution formula is summarised in Table P.1-2.

Table P.1-2. Formulation Details for PF-00446687-01 Oral Solution

Name of Ingredient	Dose Range
PF-00446687-01	
0.1 M hydrochloric Acid ^b	
Water for Irrigation (Ph. Eur.)	
Total Volume	

^a Weights are corrected for the actual potency of the batch of drug substance used.

^b The 0.1 M hydrochloric acid is manufactured by Pfizer. The specification is provided in [Section P.4.1 Specifications](#).

P.2. Pharmaceutical Development

The PF-00446687-01 oral solutions are prepared extemporaneously at the study site by two trained personnel, one of whom is a pharmacist. At study sites where a pharmacist is not available the oral solutions will be prepared extemporaneously by two trained personnel under the oversight of a Qualified Person.

During the development of the oral solution products the preparation method has been evaluated and PF-00446687-01 has been shown to completely dissolve when using the preparation procedure. The solubility of the drug substance in 0.01 M hydrochloric acid of 6.3 mg/mL is greater than the maximum concentration [REDACTED] to be used in this clinical study (Section S.1.3 General Properties).

Ensuring that the oral solutions of PF-00446687-01 are of an appropriate quality to be administered to the subject is a key concern during formulation development.

The PF-00446687-01 oral solutions used in the study will be extemporaneously prepared at the study centre and are not subjected to test prior to use. Quality and consistency of the product solutions are ensured by demonstrating that the preparation can be performed to an appropriate quality by preparing solutions over the range [REDACTED] ng/mL and [REDACTED] ng/mL. Development samples are prepared so that each solution contains a quantity of PF-00446687-01 that is weighed to be within a set tolerance of the intended content (in this case, within $\pm 1\%$ of intent). In addition, the development samples are tested (to meet the quality standards detailed in Section P.5.1 Specification), for identity, appearance, assay, (90% to 110% of intent at this stage of development) and degradation products (0.2% maximum for any individual degradation product at this stage of development). This ensures the extemporaneous preparations are of appropriate quality for administration.

Quality is also assured with the evaluation of the stability of PF-00446687-01 oral solutions across a time period, and under conditions, that adequately support the intended administrative plan for the clinical study. The testing covered chemical and physical stability when stored in polyethylene terephthalate glycol (PETG) containers. No change was observed in the appearance of the solutions and no increase in degradation products was found after at least 72 hours when stored at 2°C to 8°C. Additionally no loss in potency was observed over the time period. Results are detailed in Section P.8 Stability.

A use period of 72 hours has been assigned to the PF-00446687-01 oral solutions when stored between 2°C to 8°C in a PETG container.

The microbiological quality of the oral solution has not been assessed as it is prepared and used within a 72 hour period.

P.3. Manufacture

P.3.1. Manufacturer

PF-00446687-01 drug substance, diluents, and containers to be used at the study site will be prepared and packed in accordance with GMP at the facility described in Table P.3.1-1.

Table P.3.1-1. Site and Responsibilities for Release of PF-00446687-01

Site	Site Responsibilities
	Release testing and release of oral solution individual components

The released materials are shipped to the study site where the oral solutions will be extemporaneously prepared.

Water for Irrigation (Ph.Eur.) is sourced by the study site.

P.3.2. Batch Formula

The volume of stock solution prepared will be between [REDACTED] The oral solutions will be prepared extemporaneously at the clinical study site.

P.3.3. Description of Manufacturing Process and Process Controls

PF-00446687-01 oral solutions will be prepared extemporaneously at the study site by two trained personnel, one of whom is a pharmacist. At study sites where a pharmacist is not available the oral solutions will be prepared extemporaneously by two trained personnel under the oversight of a Qualified Person.

The required quantity of PF-00446687-01 drug substance is weighed and dissolved [REDACTED]

[REDACTED] Appropriate aliquots of the solution are dispensed into a suitable drinking vessel to achieve doses described in the clinical protocol. The aliquots are administered without further dilution.

P.4. Control of Excipients

P.4.1. Specifications

Specifications for Compendial Excipients

Water for Irrigation as described in the European Pharmacopoeia, is used.

Specifications for Non-Compendial Excipients

The specification for 0.1M hydrochloric acid is provided in Table P.4-1.

Table P.4-1. Specification for 0.1M Hydrochloric Acid

Test Procedure	Test Method	Acceptance Criteria
Appearance	Pfizer (Visual)	
Assay	Ph. Eur.	
Identification	Ph. Eur.	

P.4.2. Analytical Procedures for Non-Compendial Excipients

Not applicable to PF-00446687-01 oral solutions.

P.4.3. Validation of Analytical Procedures

Not applicable to PF-00446687-01 oral solutions.

P.4.4. Justification of Specifications

Not applicable to PF-00446687-01 oral solutions.

P.4.5. Excipients of Human or Animal Origin

None of the excipients used in the preparation of PF-00446687-01 oral solutions are of human or animal origin.

P.4.6. Novel Excipients

No novel excipients are used in the preparation of PF-00446687-01 oral solutions.

P.5. Control of Drug Product

P.5.1. Specification

At this stage of development the quality standards applied to the extemporaneously prepared PF-00446687-01 oral solutions are established to assure the safety of the preparations and to assure the appropriateness of the preparation in the proposed clinical study.

The PF-00446687-01 oral solutions are extemporaneously prepared at the study centre. As such, the extemporaneously prepared solutions are not tested to a specification.

The acceptable quality standards for the extemporaneously prepared PF-00446687-01 oral solutions are provided in Table P.5.1-1.

Table P.5.1-1. Quality Standards for PF-00446687-01 Oral Solution

Test	Test Method	Quality Standard
Appearance		
Identification		
Assay		
Individual degradation products		
Total degradation products		
NMT = Not more than		

P.5.2. Analytical Procedures

Identification, Assay and Purity Assessment

The analytical procedure used to determine identity, assay and purity of the PF-00446687-01 oral solution is the same procedure described in [Section S.4.2 Analytical Procedures, Table S.4.2-1](#).

Appearance

Visual inspection of the sample is performed.

P.5.3. Validation of Analytical Procedures

Appearance is a well-established test. Specific validation is not carried out for this method, however, the general physical properties of PF-00446687-01 have been assessed and present no difficulties to the operation of this test.

The validation of the analytical procedure used to determine identity, assay and purity of the development batch of PF-00446687-01 oral solution is described in [Section S.4.3 Validation of Analytical Procedures](#).

P.5.4. Batch Analyses

The analytical results from testing of development samples of the proposed extemporaneously prepared PF-00446687-01 oral solutions [REDACTED] are provided in Table P.5.4-1. The results demonstrate the suitability of the preparation process across the clinical dose range and show no significant absorptive losses to the container.

Table P.5.4-1. Batch Analyses for PF-00446687-01 Oral Solution Development Samples

Strength:			
Usage:		Development	Development
Site of Manufacture			
Test	Quality Standard	Result	Result
Appearance			
Identification			
Assay			
Purity			
Individual Degradation Products			
Total Degradation Products			
NMT = Not more than			

P.5.5. Characterisation of Impurities

Impurities in PF-00446687-01 drug substance are discussed in [Section S.3.2 Impurities](#) and are controlled by the specification listed in [Section S.4.1 Specification](#).

Analytical testing of development preparations of PF-00446687-01 oral solution have shown that the level of individual degradation products observed was [REDACTED] and the level of total degradation products observed was [REDACTED]. No additional degradation products were observed in PF-00446687-01 oral solutions.

P.5.6. Justification of Specification(s)

As the PF-00446687-01 oral solution is prepared extemporaneously at the study site it is not tested to a specification. However, quality standards are applied during development of the PF-00446687-01 oral solution. The focus of the quality standards applied during development is to monitor those parameters relevant to safety; therefore, the potency and purity are assessed. The quality standard applied for potency is [REDACTED] and, for purity [REDACTED] for any individual degradation product and [REDACTED] for total degradation products.

P.6. Reference Standards or Materials

PF-00446687-01 oral solutions will be prepared extemporaneously at the study site. Release testing of the oral solutions is not performed. Consequently this section is not applicable.

P.7. Container Closure System

PF-00446687-01 oral solutions will be presented in an appropriately sized PETG container.

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P.8. Stability

P.8.1. Stability Summary and Conclusions

The quality of the PF-00446687-01 oral solutions has been underwritten by evaluation of the stability of solutions across a time period, and under conditions, that support the clinical study's intended administration plan. The stability results for both solutions [REDACTED] are summarised in Table P.8.1-1 and Table P.8.1-2.

Table P.8.1-1. Results of 72 Hours In-Use Stability for [REDACTED] /mL Dose Solution

Test	Method	Quality Standard	Initial	72 Hours
Appearance	Visual Inspection	[REDACTED]	[REDACTED]	[REDACTED]
Identification	HPLC			
Assay	HPLC			
Individual Degradation Products	HPLC			
Total Degradation Products	HPLC			

NMT = not more than

Table P.8.1-2. Results of 72 Hours In-Use Stability for [REDACTED] mL Dose Solution

Test	Method	Quality Standard	Initial	72 Hours
Appearance	Visual Inspection	[REDACTED]	[REDACTED]	[REDACTED]
Identification	HPLC			
Assay	HPLC			
Individual Degradation Products	HPLC			
Total Degradation Products	HPLC			

NMT = not more than

Analytical Methods

The analytical methods used to determine assay and degradation products for the in-use stability samples are the same methods as detailed in the drug substance section, [Section S.4.2 Analytical Procedures, Table S.4.2-1](#). The appearance method is detailed in the drug product section, [Section P.5.2 Analytical Procedures](#).

Stability Summary and Conclusion

The microbial quality of the oral solutions has not been assessed as they are prepared and used within a 72 hour period.

The data presented supports the assignment of a 72 hour use period for the PF-00446687-01 oral solutions when stored in a refrigerator between 2°C and 8°C in a PETG container.

As the oral solutions are not stored for periods beyond the in-use period, stability studies to underwrite a formal shelf-life or expiry date are not performed.

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P. Drug Product (Placebo for PF-00446687-01)

P.1. Description and Composition of the Placebo

Placebos for PF-00446687-01 oral solutions to be used in clinical studies are prepared extemporaneously and contain the [REDACTED] of Denatonium Benzoate (USP) in 0.01 M hydrochloric acid.¹ Appropriate volumes of the dosing solutions to match the active dosing volumes will be dispensed into suitable drinking vessels (PETG containers). The aliquots are administered without further dilution. The placebo oral dosing solutions may be stored for a maximum of 72 hours at 2°C to 8°C.

The solution formulae are summarised in Table PL.1-1.

Table PL.1-1. Formulation Details for Placebo for PF-00446687-01 Oral Solution

Name of Ingredient	Dose Range
Denatonium Benzoate (USP)	[REDACTED]
0.1 M hydrochloric acid ^a	
Water for Irrigation (Ph. Eur.)	
Total volume	

^a The 0.1 M hydrochloric acid is manufactured by Pfizer. The specification is provided in Section P.4.1 Specifications

P.2. Pharmaceutical Development

For studies with PF-00446687-01 a bitter tasting placebo solution is used for the purpose of blinding.

Denatonium benzoate was selected due to its bitter taste at low doses. It has been evaluated and confirmed as being acceptable for use as a placebo based on safety data available in the literature. In addition, the physico-chemical characteristics of this material are suitable for use in oral solutions. The oral dosing solutions may be stored for a maximum of 72 hours at 2°C to 8°C.

Placebos for PF-00446687-01 oral dosing solution are prepared extemporaneously at the study site.

¹ The 0.01 M hydrochloric acid is prepared extemporaneously at the study center using 0.1 M hydrochloric acid solution manufactured by Pfizer and Water for Irrigation (Ph. Eur.).

P.3. Manufacture

P.3.1. Manufacturer

Denatonium benzoate, labels and containers to be used at the study site will be prepared and packed in accordance with GMP at the following Pfizer facility:

Table PL.1-2. Site and Responsibilities for Release of Components of Placebo for PF-00446687-01 Oral Solutions

Site	Manufacturing Steps
	Release testing and release of oral solution individual components.

Water for irrigation (Ph. Eur) is sourced by the study site.

P.3.2. Description of Manufacturing Process and Process Controls

Placebos for PF-00446687-01 oral solutions will be prepared extemporaneously at the study site by two trained personnel, one of whom is a pharmacist. At study sites where a pharmacist is not available the oral solutions will be prepared extemporaneously by two trained personnel under the oversight of a Qualified Person.

The required quantity of denatonium benzoate is weighed out and dissolved in 0.1 M hydrochloric acid. Water for irrigation is then added to the solution of denatonium benzoate in 0.1 M hydrochloric acid to provide the final stock solution volume as described in [P.1 Description and Composition of the Placebo](#). Individual doses are prepared by dispensing appropriate aliquots of the stock solution to match the active oral dosing solution volumes into suitable drinking vessels (PETG containers). The aliquots are administered without further dilution.

P.4. Control of Excipients

P.4.1. Specifications

Compendial excipients identified in [P.1 Description and Composition of the Placebo](#) are tested and released in accordance with the specifications and test methods described in the referenced Pharmacopoeia.

The specification for 0.1 M hydrochloric acid is summarised in Table PL.1-3.

Table PL.1-3. Specification Details for 0.1 M Hydrochloric Acid

Test Procedure	Test Method	Acceptance Criteria
Appearance	Pfizer (Visual)	
Assay	Ph. Eur	
Identification	Ph. Eur	

P.4.5 Excipients of Animal or Human Origin

None of the excipients used in the preparation of placebos for PF-00446687-01 oral solutions are of human or animal origin.

P.5. Control of Placebo

Placebo for PF-00446687-01 oral solution is extemporaneously prepared at the study site by two trained personnel one of whom is a pharmacist or where a pharmacist is not available under the oversight of a Qualified Person. As such, the extemporaneously prepared solution is not tested to a specification. The same controls on the extemporaneous preparation process are used for PF-00446687-01 oral solution and the placebo for PF-00446687-01 oral solution. The quality of the extemporaneously prepared solutions is assured in the manner outlined below.

Denatonium benzoate is a well precededented, pharmacopoeial grade excipient. The quality of the denatonium benzoate is managed by the application of its pharmacopoeial specification (USP), which establishes acceptance criteria for necessary attributes of quality.

The quality and consistency of the prepared placebo solution is further assured by application of controls on the extemporaneous preparation process, specifically by requiring that each prepared solution contains a quantity of denatonium benzoate that is weighed to be within a set tolerance of the intended content. This ensures the extemporaneous preparations are of appropriate quality for administration. The absence of PF-00446687-01 drug substance in the placebo solution is assured through the controls in the preparation procedures employed.

P.6. Reference Standards or Materials

Placebos for PF-00446687-01 oral solutions will be prepared extemporaneously at the study site. Consequently this section is not applicable.

P.7. Container Closure System for Placebo

Placebos for PF-00446687-01 oral solutions will be presented in suitably sized PETG containers.

P.8. Stability

Placebos for PF-00446687-01 oral dosing solutions will be extemporaneously prepared at the study centre and may be stored for a maximum of 72 hours at 2°C to 8°C.

P. COMPARATOR

Sildenafil citrate film-coated tablets 100 mg will be used as a comparator. These tablets have the same qualitative and quantitative composition as those commercially available as Viagra® 100 mg (Marketing Authorisation EU/1/98/077/9-12).

The comparator sildenafil citrate film-coated tablets 100 mg will be manufactured using the same manufacturing process detailed in the Viagra marketing authorisation dossier (EU/1/98/077/9-12). The comparator sildenafil citrate film-coated tablets 100 mg differ from the commercial Viagra tablets 100 mg only in their appearance. The comparator sildenafil citrate film-coated tablets 100 mg are not debossed with VGR100 and only contain the Pfizer debossing on one face of the tablets, with the opposing face plain.

P.1. DESCRIPTION AND COMPOSITION OF THE COMPARATOR

The quantitative composition of the comparator, sildenafil citrate film-coated tablets 100 mg is given in Table P.1-1.

Table P.1-1. Composition of the Comparator - Sildenafil Citrate Film-Coated Tablet 100 mg

Tablet Core		
Names of Ingredients	Unit Quantity (mg/tablet)	Reference to Quality Standards
Sildenafil Citrate		Pfizer
Microcrystalline Cellulose		Ph.Eur.
Calcium Hydrogen Phosphate (Anhydrous)		Ph.Eur.
Croscarmellose Sodium		Ph.Eur.
Magnesium Stearate		Ph.Eur.
Tablet Core Weight		N/A
Film-Coated Tablet		
Names of Ingredients	Unit Quantity (mg/tablet)	Reference to Quality Standards
Sildenafil Citrate 100 mg		N/A
Tablet Core		
Opadry® Blue (OY-LS-20921)		Pfizer ^(b)
Purified Water		USP
Opadry® Clear (YS-2-19114-A)		Pfizer ^(b)
Purified Water		USP.
Tablet Weight	N/A	
Tablet Size/Shape	Blue, round diamond-shaped tablets (14.1 mm x 10.2 mm) debossed with “Pfizer” on one side and plain on the reverse	

^(a)Equivalent to 100 mg sildenafil based on a theoretical activity of 71.2%.

^(b)Specification provided in. Section P.4.1 Specifications (Non-Compndial Excipients)

^(c)Lost during processing and does not appear in the final product.

N/A = not applicable

P.2. PHARMACEUTICAL DEVELOPMENT

Pharmaceutical development for the formulation of the comparator sildenafil citrate film-coated tablet 100 mg is contained in the Marketing Authorisation (EU/1/98/077/9-12). The minor difference in the appearance (not debossing with VGR100) does not impact the dissolution profile, consequently dissolution data are not provided.

P.3. MANUFACTURE

P.3.1. Manufacturers

The addresses of the manufacturing or release sites for sildenafil citrate film-coated tablets 100 mg are provided in Table P.3.1-2.

Table P.3.1-2. Manufacturing Sites and Responsibilities for Release of the Comparator, Sildenafil Citrate Film-Coated Tablets 100 mg

Site	Site Responsibilities
	Manufacture and release testing
	Packaging and final release

P.3.2. Batch Formula

The batch size may vary depending on clinical demands. Current batch sizes are within the range of [REDACTED] of common blend. [REDACTED]

Table P.3.2-1 Formula for a [REDACTED] Batch of Sildenafil Citrate Film-Coated Tablets 100 mg

Name of Ingredient	Reference to Quality Standard	Quantity Required (g)
Sildenafil Citrate	Pfizer	
Microcrystalline Cellulose	Ph. Eur.	
Calcium Hydrogen Phosphate (anhydrous)	Ph. Eur.	
Crosscarmellose Sodium	Ph. Eur.	
Magnesium Stearate	Ph. Eur.	
Opadry Blue	Pfizer ²	
Opadry Clear	Pfizer ²	

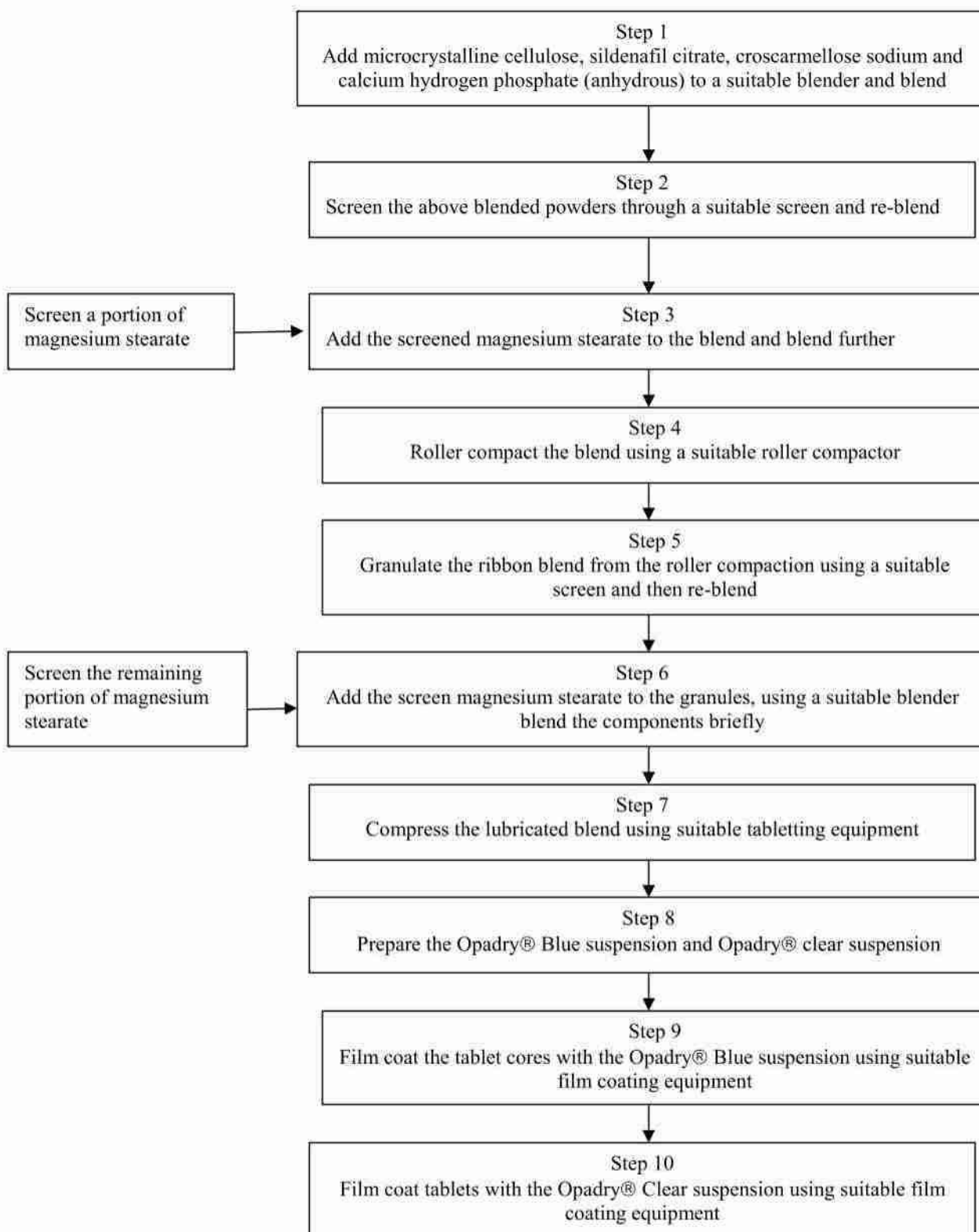
¹ 25% Used pre-roller compaction and 75% used post roller compaction

² Specifications provided in Section P.4.1 Specifications (Non-compendial Excipients)

³ An excess of both blue and clear coating suspensions are prepared and coating continues until a 2.5 %w/w blue coat and a 0.75 %w/w clear coat have been added sequentially

P.3.3. Description of Manufacturing Process and Process Controls

Flow diagram for the manufacturing process for comparator tablet is outlined below:



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P.4. CONTROL OF EXCIPIENTS

P.4.1. Specifications

Compendial Excipients

Microcrystalline cellulose, croscarmellose sodium and calcium hydrogen phosphate (anhydrous) and magnesium stearate, all meet the requirements of the Ph. Eur. Purified Water meets the requirements of the USP.

Non-Compendial Excipients

Table P.4.1-1 Composition of Opadry® Blue (OY-LS-20921)

Name of Ingredient	Reference to Quality Standard	% w/w
Lactose Monohydrate	Ph. Eur.	
Hydroxypropyl methylcellulose 2910 (15 cP)	Ph. Eur.	
Titanium Dioxide (E 171)	Ph. Eur.	
Glycerol Triacetate	Ph. Eur.	
Indigo Carmine Aluminium Lake (FD&C Blue No. 2)	E132	

Table P.4.1-2 Test and Acceptance Criterion for Opadry® Blue (OY-LS-20921)

Test	Procedure	Acceptance criterion
Appearance		
Identity		
Residue on ignition		
Heavy metal		

Table P.4.1-3 Composition of Opadry® Clear (YS-2-19114-A)

Name of Ingredient	Reference to Quality Standard	Name of Ingredient
Hydroxypropyl methyl cellulose 2910 (15cP)	Ph. Eur.	
Glycerol Triacetate	Ph. Eur.	

Table P.4.1-4 Test and Acceptance Criterion for Opadry® Clear (YS-2-19114-A)

Test	Procedure	Acceptance criterion
Appearance		
Identity		
Residue on Ignition		
Heavy Metals		

P.4.2. Analytical Procedures

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.4.3. Validation of Analytical Procedure

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.4.4. Justification of Specifications

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.4.5. Excipients of Human or Animal Origin

The magnesium stearate used in the comparator sildenafil citrate film-coated 100 mg tablets is of vegetable origin.

The lactose monohydrate used in the comparator sildenafil citrate film-coated 100 mg tablet formulation is a milk derivative and is classified as a Category I (no detectable infectivity) excipient in the CPMP Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products EMEA/410/01.

P.4.6. Novel Excipients

There are no novel excipients used to manufacture the comparator.

P.5. CONTROL OF THE MODIFIED COMPARATOR

P.5.1. Specification(s)

The specification and acceptance criteria for the comparator sildenafil citrate film-coated tablets 100 mg are given in Table P.5-1-1

Table P.5.1-1. Specification for Sildenafil Citrate Film-Coated Tablets 100 mg

Test	Method	Acceptance Criteria
Visual Identity		
Sildenafil Identity (IR)		
Citrate Identity (HPTLC)		
Assay (HPLC)		
Dissolution (15 minutes)		
Content Uniformity	USP <905>	
Water Content		
Total Degredation products		

P.5.4 BATCH ANALYSES

Certificates of Analysis for representative batches are appended to the appendix.

P.6. REFERENCE STANDARDS

This information can be found in the Marketing Authorisation EU/1/98/077/9-12.

P.7. CONTAINER CLOSURE SYSTEM FOR COMPARATOR

The sildenafil citrate film-coated tablets 100 mg will be packaged in HDPE bottles with child resistant caps.

P.8. STABILITY

Details of the sildenafil citrate film-coated tablets 100 mg (Viagra 100) are contained in the Marketing Authorisation Application approved by the European Agency for the Evaluation of Medicinal Products (ref EU/1/98/077/9-12). These tablets have been assigned a shelf-life of five years when packed in HDPE containers and stored at or below 25°C.

The tablets proposed for the clinical trial differ only from Viagra® tablets with respect to tablet debossing. A shelf life of five years has therefore been assigned to the product based on the extensive historical data available on the Viagra® product.

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P. Placebo

P.1. Description and Composition of the Placebo for Comparator

The placebo tablet for the study is a blue rounded, diamond shaped film coated tablet with “Pfizer” debossed on one side. The components and quantitative composition of the placebo are given in Table PL.1-1.

Table PL.1-1. Complete Composition for Placebo for Sildenafil Citrate 100 mg Film-coated Tablets

Component	Function	Compendial Grade	Unit Composition mg/tablet
Lactose, hydrous, spray dried	Diluent		
Microcrystalline cellulose	Diluent		
Magnesium Stearate	Lubricant		
Blue Opadry® (OY-LS-20921) ^a	Colorant		
Clear Opadry® (YS-2-19114-A) ^a	Colorant		
Purified Water ^b	Vehicle	USP	
Total		N/A	

^a For list of components, refer to the active comparator section, P.4 Control of Excipients, Table P.4.1-1 and Table P.4.1-3.

^b Not present in final dosage form.

P.2. Pharmaceutical Development (Placebo for Sildenafil Citrate Tablets)

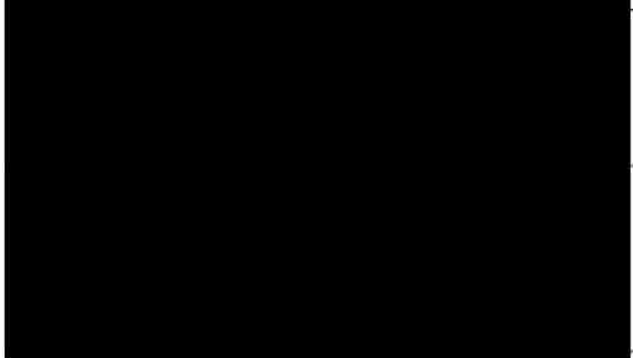
All excipients used in manufacturing the placebo for sildenafil citrate are well precededented pharmaceutical excipients for use in tablets.

P.3. Manufacture

P.3.1. Manufacturer (Placebo for Sildenafil Citrate Tablets)

Placebo clinical supplies were manufactured and released at the following locations identified in Table P.3.1-1.

Table P.3.1-1. Site and Responsibilities for Release of Components of Placebo for Sildenafil Citrate Tablets

Site	Responsibilities
	Manufacturing and release testing
	Packaging and release testing Release

Method of Manufacture

Microcrystalline cellulose, lactose (hydrous, spray dried) and magnesium stearate are blended. The blend is then compressed using diamond-shaped tooling with an upper punch debossed with “Pfizer” and a plain faced lower punch. The placebo tablet core is then aqueous film coated with blue Opadry® (OY-LS-20921) followed with clear Opadry® (YS-2-19114-A).

P.4. Control of Excipients

The information on compendial and noncompendial excipients used in the manufacture of placebos for sildenafil tablets are described in [section P.4 Control of Excipients](#) for the active comparator.

P.5. Control of Placebo (Placebo for Sildenafil Citrate Tablets)

The release specification for sildenafil citrate placebo tablets is provided in Table PL-2.

Table PL-2. Specification for the Placebo for Sildenafil Citrate Tablets

Test	Acceptance Criteria
Appearance	
Identification (IR)	
Identification (TLC)	

P.6. Reference Standards or Materials (Placebo for Sildenafil Citrate Tablets)

Not applicable for placebo.

P.7. Container Closure System for Placebo

Placebo for sildenafil citrate tablets is packaged in HDPE bottles with heat induction seal and child-resistant closures.

P.8. Stability

Sildenafil citrate tablets packaged in HDPE bottles with heat induction seal and child resistant closures have been assigned a shelf life of five years.

A.2. Adventitious Agents Safety Evaluation

Non-Viral Adventitious Agents

PF-00446687-01 Oral Solution

All of the components used in the preparation of the PF-00446687-01 oral solution comply with the EMEA Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01 and do not contain specified risk materials.

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BAT 61 SECRETARIA

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Pfizer PCM
Site d'Amboise
Z.I. Port sur Cisse - BP 109
F-37401 Amboise Cedex France
Tél. : (+33) 2 47 23 77 78 - Fax : (+33) 2 47 23 79 80



Pfizer Global Manufacturing

CERTIFICATE OF ANALYSIS

SILDENAFIL 100 mg Tablets CLIN BULK
1443VRC

LOT N°5181703

Manufacturing date : Sept. 22, 2005

Expiry date :

The average results of our tests are as follows :

DETERMINATIONS

Sildenafil content (blend) (HPLC)
Content uniformity (blend)
Appearance (Cores)
Weight variation
Hardness of cores
Appearance (Tablets)
Sildenafil identification (IRFT)
Water content (KF) (Tablets)
Weight variation (Tablets)
Sildenafil content per tablet (HPLC)
Dissolution rate (30mn)
Citrate identification (HPLC)
Indigotin identification
Titanium dioxide identification
Enterobacteriaceae count
Microorganism count
Mould and yeast count
Absence of: E.Coli/ Pseudo.A/ Staph Aureus/ Salmonel

SPECIFICATIONS

RESULTS

This product was manufactured in accordance with European GMP and only for clinical trials. This product cannot be distributed for commercial use

Name: [REDACTED]
Function: Quality Assurance Assistant

Printing Date : Nov 07, 2005

Pharmacist Visa

Pfizer Global Manufacturing
Amboise France
ASSURANCE QUALITE

07 NOV. 2005

Object Id 090120208014059e

Printed On 02-Apr-2007

Approved



Pharmaceutical Sciences
Global Research & Development
Formulated Drug Product Analytical Test Report
Certificate of Analysis

Page 1 of 1

Product/Device Name	Placebo for Sildenafil Citrate 100 mg Tablets		
Lot Number		Lot Number	05-032673



Test	Acceptance Criteria	Test Result
1 Identification (Appearance)		Meets test
2 Identification (IR)		Meets test
3 Identification (TLC)		Meets test

Object Id 0901202080152a81

Printed On 13-Mar-2007

Approved

4.2.2. NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY DATA

For summaries of the non-clinical pharmacology and toxicology data please refer to Section 5 of the Investigator's Brochure, found in part 4.1 of this application.

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4.2.3. PREVIOUS CLINICAL TRIAL AND HUMAN EXPERIENCE DATA

For summaries of the previous clinical trial and human experience data please refer to Section 6 of the Investigator's Brochure, found in part 4.1 of this application.

4.2.4 OVERALL RISK-BENEFIT ASSESSMENT

1. Potential Benefits

Male erectile dysfunction (MED) is a condition that, in moderate or severe form, affects around 35% of men over the age of 40 (Feldman et al., 1994). Current treatment options include phosphodiesterase Type 5 inhibitors such as sildenafil, tadalafil, and vardenafil and these are effective in around 70% of patients. Although well tolerated, these drugs have dose-limiting side effects such as headache, facial flushing, and back pain. Furthermore, this class of drugs is contraindicated with nitrate therapy which is often used for the treatment of coronary heart disease; MED and coronary heart disease frequently co-exist. There is a need for new agents with increased efficacy, that are free of dose-limiting side effects and are available to a wider population of men.

The melanocortin family of related peptide neurotransmitters (MC1, MC2, MC3, MC4, and MC5) regulate a wide range of physiological actions. The endogenous ligand of the melanocortin receptors is α -MSH (melanocyte stimulating hormone), a 13 amino acid peptide derived from pro-opiomelanocortin. That melanocortins can influence male and female sexual behaviour and penile erection in animals has been known for almost 40 years, and indices of erectile activity evoked by ACTH or α -MSH have been documented in a range of species from rodents to primates. A number of non-specific melanocortin agonists have been reported to elicit pro-sexual effects in the clinic. Melanotan-II has evoked spontaneous erections and heightened sexual desire in men with erectile dysfunction (Wessells et al., 2000(a) & (b)). Another non-selective agent, PT-141 (bremelanotide), is currently in phase 2 development for both male and female sexual dysfunction, having reported positive effects in biomarker studies (Diamond et al., 2004; Diamond et al., 2006) and Phase 2.

PF-00446687 has demonstrated activity in three animal models of sexual behaviour; the two male models are directly relevant here. The models used to determine efficacy in males were penile erectile function in conscious telemetered rats and changes in intracavernosal pressure following dorsal penile nerve stimulation in anaesthetised rats. In the rat model of erection, PF-00446687 increased the number of spontaneous penile erections observed in a dose-dependant manner. In the anaesthetized rat model of penile erection, where the dorsal penile nerve is electrically stimulated, effects (measured as an increase in the AUC corrected for systemic BP) were observed at 3 different stimulation frequencies following IV dosing with PF-00446687. In a clinical biomarker study conducted with PF-00446687 in healthy male volunteers using the Rigiscan (penile plethysmography) technique, 200 mg PF-00446687 demonstrated improvement over placebo during visual sexual stimulation. Notably, unlike the non-specific melanocortin agonists where nausea is dose limiting with an incidence of approximately 15% (Wessells et al., 2000a; Wessells et al., 2000b; Diamond et al., 2004), no emesis was observed in this biomarker study.

These data suggest that selective MC4 receptor agonism could provide an improved therapeutic window in comparison with other melanocortin agonists.

Dose Rationale

Non-clinical models of sexual behaviour provided the rationale for the initial development of specific MC4 agonists. The dose range explored [REDACTED] in the clinic has been well-tolerated. The biomarker study of erectile activity has demonstrated activity at 200 mg in healthy volunteers. Additionally, adverse events that are believed to be pharmacologically driven (restlessness, yawning, stretching) have been reported at 195 mg. Hence, 200 mg will be used as the initial dose for confirmation of activity in patient populations and the activity of lower doses will subsequently be explored.

2. Potential Risks

A total of 64 subjects (all males) have received PF-00446687 (of which 52 have received doses of 195 or 200 mg) and 63 subjects have received placebo in the two completed studies. The initial route of administration was sub-lingual dosing, but due to poor local toleration, the oral route is now being pursued. Overall, PF-00446687 has been well-tolerated upon single dose administration with no discontinuations due to adverse events nor any serious adverse events in the program.

Following sublingual dosing, peak plasma concentrations were achieved within 2 to 8 hours, exposure increased supra-proportionally with increasing dose (<2-fold relative to dose), and terminal half-life was approximately 12 hours across the entire dose range. Following oral dosing, exposure was similar to that achieved for sublingual dosing at comparable dose levels, however, the small sample size (n = 4) needs to be considered. Urinary excretion was negligible with <2.5% dose excreted as parent over 48 hours after dosing. There were no discernible differences between the 195 mg dose of PF-00446687 and placebo for any of the pharmacodynamic markers evaluated (TSH, LH, FSH, GH and prolactin).

A total of 52 subjects have received 195 or 200 mg single-dose to date and there have been no safety issues of concern. The top dose has been limited by the observation of convulsions in mice, rats and dogs at high exposures. The lowest exposure at which convulsions occurred was in the 1-month rat study where a single animal was affected (9 mg/kg) towards the end of the study. No convulsions were observed in rats at 3 mg/kg (C_{max} 317 ng/mL total, 22.2 ng/mL free). In humans, 195 mg has an associated C_{max} of approximately 31 ng/mL total (3.9 ng/mL, 8.3 nM free). At 9 mg/kg in rats, there is approximately a 10-fold margin over the C_{max} (free) at the highest dose being investigated in the clinic (200 mg). In this single dose study, it is not anticipated that unbound plasma concentrations would exceed 10 nM. Future toxicology studies are aimed at refining this upper limit. Investigators will be advised to exclude those subjects with a history of seizures.

In the clinic, sublingual administration was poorly tolerated; reports included application site anaesthesia/irritation and hypoesthesia. The sublingual route is no longer being pursued. Across both studies, the most common treatment-related systemic adverse events were restlessness (6.3%), increased libido (3.1%), somnolence (3.1%), dizziness (3.1%); both nausea (6.3%) and abdominal pain (3.1%) were mostly reported with sublingual dosing. There have been no clinically meaningful changes in laboratory tests, vital signs or ECG

parameters that could be attributed to study drug. There have been no discontinuations due to adverse events nor any serious adverse events in the PF-00446687 program.

Animal studies indicate that PF-00446687 may have had a mild vasodilator action in dogs at unbound plasma concentrations at and above 15.5 nM (7.3 ng/mL), resulting in dose-related reductions in blood pressure (<10 mmHg), small reflex increases in myocardial contractility, increase in heart rate (up to 12 bpm) and reduction in PR interval; no QTc effects were noted. The concentrations previously explored in the clinic, and those expected in the proposed single dose study, are below those at which the non-clinical cardiovascular effects were observed. No clinically relevant changes in vital signs have been observed in either of the two clinical studies conducted to date.

The effects of PF-00446687 on urine and electrolyte excretion were investigated in a rat model at doses up to 10 mg/kg IV. At 1 mg/kg ($C_{max,u}$ of 13.5 nM, 6.4 ng/mL), significant increases in urine volume and electrolyte (Na^+ , K^+ , and Cl^-) secretion were observed; this effect was further amplified at 10 mg/kg IV. In the 1-month IV study, haemoconcentration was observed in dogs from the IV dose of 3 mg/kg. Urinary creatinine, osmolality, volume and electrolytes (sodium, potassium, chloride) were monitored in the first-in-human study and there were no dose-related changes of note.

The predominant clearance pathway for PF-00446687 is expected to be metabolism by cytochrome P450 3A4; in vitro data also indicate a potential inhibition of cytochrome P450s 3A4 and 2C19 by PF-00446687 at higher concentrations. These data suggest a high potential for drug-drug interactions; wherein PF-00446687 could act as the victim (where CYP 3A4 is inhibited by another agent and exposures to PF-00446687 are increased) or as the perpetrator (where PF-00446687 could itself alter CYP3A4 activity and therefore the exposure of other substrates). The impact of these interactions will need to be assessed within the context of the therapeutic index. An assessment of the impact of CYP 3A4 inhibition (by ketoconazole) on the pharmacokinetics of PF-00446687 is currently ongoing. For the proposed single dose study, potential drug-drug interactions will be limited by the inclusion/exclusion criteria.

Fertility and teratology studies with PF-00446687 have not been conducted to date.

3. Risk Benefit Statement

On the basis of the benefit and risk assessments outlined above, it is considered that there is a favourable benefit-risk ratio for studying the safety and efficacy of PF-00446687 at single doses up to 200 mg in MED male patients. Sildenafil is being used in this study as a positive control fully within the terms of its market authorization and its use does not alter the risk-benefit profile.

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