CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214793Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 214793 IQA

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QUALITY ASSESSMENT

Recommendation: ***Approval***

NDA [214793]

PyLarify (piflufolastat F 18) injection

Review #[FINAL]

Drug Name/Established Name; Dosage Form	PyLarify (piflufolastat F 18) injection; Sterile solution
Strength(s)	37 MBq – 2960 MBq/mL (1 – 80 mCi/mL) (b) (4)
Route of Administration	IV injection
Rx/OTC Dispensed	Rx
Applicant	Progenics Pharmaceuticals, Inc., New York, NY 10007
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED (seq. no.)	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Origional NDA 214793	9/29/2030	OPQ-CMC, Microbiology, Process/Facilities (OPF)

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Martin Haber	Su Tran
Drug Product	Christopher Galliford	Danae Christodoulou
Process/Facilities	Laurie Nelson	Vidya
Microbiology	Jennifer Sykora	Yan Zheng
Environmental	Christopher Galliford	Danae Christodoulou
RBPM	Anika Lalminsingh	N/A
Application Technical Lead	Eldon E. Leutzinger	N/A

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs: N/A

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	V	(b) (4)		Adequate	4/20/2021	N/A

Other supporting DMF's include (b) (4)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
[18F]DCFPyL, Progenics	129952	active

2. CONSULTS

DISCIPLINE	RECOMMENDATION	DATE	REVIEWER
N/A			

Executive Summary

I. Overall Recommendation on Approvability

OPQ recommends [**APPROVAL**] of NDA [214793] for commercialization of [PrPyLarify (piflufalostat F 18) injection], 9 mCi per dose at TOA and strength of ≤ 80 mCi/mL (chemical mass of ≤ 4 µg) with NMT 7.89% Ethanol in 0.9% Sodium Chloride for Injection and expiration dating period of [10] hours:

- The applicant [has] provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product
- The Office of Process and Facility has made a recommendation of [approval] for all the facilities involved in this application.
- The proposed labeling and labels [have] adequate information to meet the regulatory requirements.

II. Product Quality Review Context

Indication and Intended Population:
PyLarify is indicated for positron emission tomography (PET) of prostate-specific membrane antigen PSMAP lesions in men with prostate cancer

- With suspected metastasis who are candidates for therapy
- With suspected recurrent based on elevated PSA

Regulatory Context - Designation of Drug Substance:
2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)amino]pentyl}ureido)-pentanedioic acid
$C_{18}H_{23}{}^{18}FN_4O_8$
Molecular weight:
^{18}F (β^+, 0.635 MeV, max; $\gamma^{\pm}$, 511 KeV, 134%; $t_{1/2}$ 109.7 min)

The chemical structure of ^{18}F-DCFPyL is show in the following taken from the NDA (Section 3.2.S.1.2, Figure 2).


structure.pdf

The drug substance in PyLarify (piflufolastat F 18)injection is that substance which is radioactive, **2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)amino]pentyl}ureido)-pentanedioic acid** that *"is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, …of disease…"* (21 CFR 314.3)]. The image result is driven by both biodistribution of the chemical system (containing the radionuclide), and the radionuclidic properties of ^{18}F. The science is clear here, creating a basis for *2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)amino]pentyl}ureido)-pentanedioic acid* as the entity that furnishes the "action" expected of a drug substance.

Regulatory Context - Regulatory Status of the Precursor:
(b) (4)
[redacted]
Together, all of these factors raise the controls for the Precursor to the level of scrutiny for an API.

Product Profile and Critical Quality Attributes (CQA's):
The product consists of a formulation of 2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)amino]pentyl}ureido)-pentanedioic acid with NMT 7.8% Ethanol in Saline. (b) (4) [redacted]
The dose consists of 9 mCi @ TOA and chemical mass ≤ 4 µg. The CQA's are comprised of the standard panel of attributes for PET radiopharmaceuticals with those pertaining to the radionuclide and its residence in the organic molecule (Radiochemical Identity, Radiochemical Purity, Radionuclidic Identity, Radionuclidic Identity, Specific Activity and Strength) with nothing particularly unique as arising from structural considerations, radionuclide or other physicochemical properties characterizing this chemical system.

Areas of Unique Focus:
There is nothing unique noted in the manufacturing process, control of materials or quality controls, all of these areas closely following standard procedures for PET radiopharmaceuticals. However, what stands out needing attention is the **Comparability Protocol (CP)** proposed by the applicant. **That is because some change is a natural course of events to be expected and it is the CP that becomes the guiding principle for how to handle these changes within the regulatory landscape**. Based on this criticality, its discussion is placed in a special section under the Summary of Quality Assessment.

III. Summary of Quality Assessments

The Summary of Quality Assessments are comprised of four major areas (Drug Substance, Drug Product, Microbiology and Facilities) organized chronologically. Drug Product is divided into appropriate sub-sections. Labeling is being included within the Drug Product, since it specifically pertains to the marketed end-product of manufacture. And, although Microbiology and Facilities impact drug product quality (within the **integrable whole**), they are being here left as independent entities with the understanding that many of the issues within each crosscut with the general landscape of CMC.

Drug Substance
A prominent feature that makes radiopharmaceuticals unique among drug products is the presence of the radionuclide making **2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)amino]pentyl}ureido)-pentanedioic acid** with the radionuclide the active ingredient and active moiety and thereby the "actual" drug substance. (b) (4) [redacted]

(b) (4)

[redacted]

(b) (4)

All resolved.

Drug Product

The totality of CMC issues identified in this NDA from comments sent February 5, 2021, and responses received February 19, 2021) can be divided into the following categories:

- **Controls of Materials** (b) (4) [redacted]. Identity testing and assay for excipients are critical, since excipients are among the components of the drug product. Identity goes in hand with that since it contributes to the assurance of drug product integrity, that the components going into the drug product are what is intended for the formulation/composition. Assay is critical as it contributes to the overall drug product quality, introducing nothing not intended, and aiding assurance that the release

specifications for each batch of drug product produced meets the drug product release specifications.

The container closure system is an established part in the controls of materials, that it is fully defined and meets specifications for what is expected to be used with a product for human administration. Its use (b) (4) is an issue pertaining to labeling, but appropriately included within this section since size of the container comes into play with size of dose engendering an array of CMC issues, appropriately cross cutting with CMC and therefore justifying its location within the control of materials. In the context of Comment 7, that it is accurately denoted in the labeling depends on its description being well-defined and with the appropriate specifications (CMC).
Resolved.

- **Release Specifications** (b) (4)

Resolved.

- **Analytical Controls** (b) (4)

Resolved.

Analysis by ATL:

(b) (4)

- **Stability** (at the lower and upper ends of ***range of radioactivity concentration***, 1 – 80 mCi/mL – Comment 5). In the Progenics IND 129952, there was data for batch size (manufactured at (b) (4)) of about (b) (4) Ci and around (b) (4) mCi/mL radioactivity concentration (strength) and was found to be stable over a period of 10 hours of storage

at room temperature, thus serving as precedent for the expectations for production batches under the NDA. The batch size produced for the NDA studies was also at the (b) (4) Ci scale at around (b) (4) mCi/mL and storage at room temperature for 10 hours, fitting within the specification range of 1 – 80 mCi/mL. **In these regards, it is standard policy to request stability at the upper end of the RAD concentration range (listed in the release specification) for radiopharmaceuticals**.

Analysis by ATL:

(b) (4)

Stability at the lower end provides a kind of benchmark upon which to judge the results from the upper end of the range. With responses from the applicant, all issues within Comment #5 are **Resolved**.

- **Comparability Protocol**

(b) (4)

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(b) (4)

Resolved.

Labeling

USAN

(b) (4)

The INN Expert Committee revised it to "piflufolastat," based on its structure similar to iofolastat (123I), another PSMA-targeting diagnostic agent, which has been accepted by USAN. This revision has been accepted by Progenics and labeling provided with the latest revision. **Resolved**.

Microbiology

The essential role of microbiology in parental drug manufacture is the control of microbial contamination through assurance (1) that materials used in the manufacture and those that come into contact with the drug product meet the appropriate standards, and that (2) equipment and processes support drug product quality. In this context, there were multiple issues identified in the review by microbiology (Jennifer Sykora, Ph.D.) and broadly covering major areas of the production of product (b) (4)

. All these issues are **Resolved**.

Facilities

The (b) (4) inspection is completed and the recommendation is for approval (OPMA). And the Sofie manufacturing site is recommended for approval (OPMA). There are no outstanding issues for Process and all facilities are recommended for approval by OPMA and from ORA. Refer to the Process/Facilities review (4/14/2021) for a detailed account of all issues and their resolution.

IV. Final Analysis of Product Quality Review Issues (~200 words per issue)

No issues remain from the primary reviews from CMC (Chemistry, Manufacturing and Controls) Product Quality, Microbiology Product Quality and Manufacturing Facility Inspection standpoints. PyLarify Injection meets all applicable standards to support the identity, strength, quality and purity that it purports.

I. Summary Basis for Product Quality Recommendation (150 words)

There are no remaining issues from the primary reviews from CMC (Chemistry, Manufacturing and Controls) Product Quality, and Microbiology Product Quality

concerning the identity, strength, quality and purity of PyLarify Injection. Facility reviews have been completed and the review from OPF is in panorama, recommending approval of NDA 212793.

II. Lifecycle Considerations

There are no important future lifecycle considerations.

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(b) (4)

For additional information, see the FDA "Guidance for Industry: Changes to an Approved NDA or ANDA" (April 2004).

Progenics Response:
Progenics acknowledges the Guidance and will revise the Comparability Protocol as recommended by the Agency.

Reviewer's assessment: Acceptable.

OVERALL ASSESSMENT AND SIGNATURES: DRUG PRODUCT

Reviewer's Assessment and Signature:
ADEQUATE
Christopher Galliford, Ph.D., 4/16/2021

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.
Danae Christodoulou, Ph.D., 4/16/2021

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

The applicant states that this submission qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(a) and 25.15. To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

Reviewer's Assessment: Adequate.

In accordance with 21 CFR 25.30 (m), Progenics Pharmaceuticals, Inc. claims a categorical exclusion from the requirement to prepare an Environmental Assessment as the low-level and rapidly decaying radioactive waste materials (as defined in the Nuclear Regulatory Commission regulations at 10 CFR 61.2) and chemical waste materials generated in the laboratories serviced by the contracts administered by FDA, will be disposed of in compliance with all applicable Federal, State, and local requirements.

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL

Reviewer's Assessment and Signature:
ADEQUATE
Christopher Galliford, Ph.D., 4/16/2021

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.
Danae Christodoulou, Ph.D., 4/16/2021

I. Review of Common Technical Document-Quality (Ctd-Q) Module 1

Labeling & Package Insert

1. Package Insert

The package insert is a user's guide in the form of a booklet.

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	(b) (4) (b) (4) (b) (4) Injection (piflufalostat F-18).	**Adequate**
Dosage form, route of administration	Intravenous.	**Adequate**
Controlled drug substance symbol (if applicable)	Not required.	**Adequate**
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	(b) (4) injection.	**Adequate**

Conclusion: Adequate

(b) "Full Prescribing Information" Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

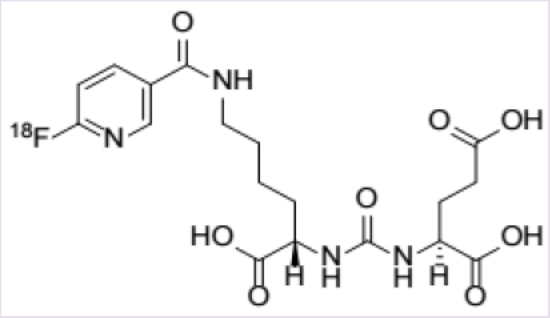
(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	(b) (4)	**Adequate**
Strengths: in metric system		**Adequate**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear, colorless (b) (4) solution for injection.	**Adequate**

Conclusion: Adequate

#11: Description (21CFR 201.57(c)(12))

(b) (4)



(b) (4)

Item		Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name		Provided.	**Adequate**
Dosage form and route of administration		Provided.	**Adequate**
Active moiety expression of strength with equivalence statement for salt (if applicable)		Provided.	**Adequate**
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		Provided.	**Adequate**
Statement of being sterile (if applicable)		Not required.	**Adequate**
Pharmacological/ therapeutic class		Provided.	**Adequate**
Chemical name, structural formula, molecular weight		Provided.	**Adequate**
If radioactive, statement of important nuclear characteristics.		Not required.	**Adequate**
Other important chemical or physical properties (such as pKa, solubility, or pH)		Provided.	**Adequate**

Conclusion: Adequate

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

(b) (4).

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	(b) (4)	Adequate
Available units (e.g., bottles of 100 tablets)	(b) (4)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided.	Adequate
Special handling (e.g., protect from light, do not freeze)	Provided.	Adequate
Storage conditions	Provided.	Adequate

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Progenics Pharmaceuticals Inc.	Adequate

Conclusion: Adequate

2. Container and Carton Labeling

1) Immediate Container Label

(b) (4)

Reviewer's Assessment: **Adequate.**

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	**Adequate**
Strength (21 CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	(b) (4)	**Adequate**
Route of administration 21.CFR 201.100(b)(3))	(b) (4) .	**Adequate**
Net contents* (21 CFR 201.51(a))	(b) (4)	**Adequate**
Name of all inactive ingredients (; Quantitative ingredient information is required for injectables) 21 CFR 201.100(b)(5)**	(b) (4)	**Adequate**
Lot number per 21 CFR 201.18	Provided	**Adequate**
Expiration date per 21 CFR 201.17	Provided	**Adequate**
"Rx only" statement per 21 CFR 201.100(b)(1)	Provided	**Adequate**
Storage (not required)	Provided	**Adequate**
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Provided	**Adequate**
Bar Code per 21 CFR 201.25(c)(2)***	Provided	**Adequate**
Name of manufacturer/distributor (21 CFR 201.1)	Provided	**Adequate**
Warnings	(b) (4)	**Adequate**

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.

**For solid oral dosage forms, CDER policy provides for exclusion of "oral" from the container label

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: Adequate.

2) Carton Labeling

While the drug product presentation does not technically include a carton, the lead shield has a similar label to that of the drug product vial above:

(b) (4)

Note that the

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	N/A.	Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100((d)(2))	N/A.	Adequate
Net contents (21 CFR 201.51(a))	N/A.	Adequate
Lot number per 21 CFR 201.18	N/A.	Adequate
Expiration date per 21 CFR 201.17	N/A.	Adequate
Name of all inactive ingredients (except for oral drugs); Quantitative ngredient information is required or injectables)[201.10(a), 21CFR201.100(d)(2)]	N/A.	Adequate
Sterility Information (if applicable)	N/A.	Adequate
"Rx only" statement per 21 CFR 201.100(d)(2), FD&C Act 503(b)(4)	N/A.	Adequate
Storage Conditions	N/A.	Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all abels or labeling), also see 21 CFR 207.35(b)(3)	N/A.	Adequate
Bar Code per 21 CFR 201.25(c)(2)**	N/A.	Adequate
Name of manufacturer/distributor	N/A.	Adequate
"See package insert for dosage nformation" (21 CFR 201.55)	N/A.	Adequate
"Keep out of reach of children" (optional for Rx, required for OTC)	N/A.	Adequate
Route of Administration (not equired for oral, 21 CFR 201.100(d)(1) and (d)(2))	N/A.	Adequate

Conclusion: Adequate.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:
ADEQUATE
Christopher Galliford, Ph.D., X/X/2020

Secondary Review Comments and Concurrence:
I concur with the reviewer's assessment.

Danae Christodoulou, Ph.D., 4/16/2020

Christopher Galliford

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Danae Christodoulou

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	214793
Assessment Cycle Number	01
Drug Product Name/ Strength	(b) (4) F18 Injection)
Route of Administration	Intravenous
Applicant Name	Progenics Pharmaceuticals, Inc., One World Trade Center, 47th Floor, Suite J, New York, NY 10007, USA
Therapeutic Classification/ OND Division	OND/OSM/DIRM
Manufacturing Sites	• (b) (4) • SOFIE Co. dba SOFIE, 100 Executive Drive, Suite 4, Sterling, VA 20166 USA
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001	**9/29/2020**
0007	**1/22/2021**
0011	**2/5/2021**

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: None

Concise Description of Outstanding Issues: None

Supporting Documents:

- **Microbiology review (b) (4).doc (dated 2/9/2016, Recommended for Approval) for media fill protocols at (b) (4) facilities.**
- **Microbiology review (b) (4).docx (dated 4/20/2018, Recommended for Approval) for media fill studies.**

P.1 Description of the Composition of the Drug Product

- **Description of drug product** (See 3.2.P.1 in "Description and Composition of the Drug Product – Description of the Dosage Form") – The 18F-DCFPyl injection is supplied as a clear, colorless, particulate-free, sterile, pyrogen free (b) (4) solution, in a multi-dose 50 mL vial with 20 mm rubber stopper and aluminum seal. The nominal volume of the final drug product (DP) is ~ 50 mL and the radioactivity concentration (b) (4) is ≤ 80 mCi/mL. The proposed shelf life is 10 hours.

- **Drug product composition** (See 3.2.P.1 in "Description and Composition of the Drug Product – Composition - General") –

Ingredient	Function	Quantity per Dose
18F-DCFPyL	API	9 mCi @ time of administration (≤ 4 µg chemical mass)
Ethanol, (b) (4)	(b) (4)	1-7.89% w/v
Normal saline, USP		(b) (4)

- **Description of container closure system** (See 3.2.P.1 in "Description and Composition of the Drug Product – Container Closure System" and see 3.2.P.7 in "Container Closure System") –

Component	Description	Manufacturer
Vial		(b) (4)
Rubber Stopper		
Aluminum Seal		

(b) (4) The firm provided a Letter of Authorization, dated Feb 1, 2019, for reference to DMF# (b) (4). A Letter of Authorization is provided to reference this DMF (dated May 18, 2020). The DMF is not reviewed because the final vial assembly is considered the final drug product and all production and validation studies regarding the final drug product are contained within the current submission.

Reviewer's Assessment: ***Adequate***

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

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