# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 212155Orig1s000

# PRODUCT QUALITY REVIEW(S)


# Office of Pharmaceutical Quality

New Drug Application (NDA) **212155**

Integrated Quality Assessment

# Contents

# QUALITY ASSESSMENT

**Recommendation: *Approval***

# NDA [212155]

# Fluoroestradiol F 18 Injection

# Review #[FINAL]

| | |
|---|---|
| Drug Name/Dosage Form | CERIANNA (Fluorestradiol F 18 Injection) / Aqueous solution |
| Strength(s) | 148-3700 MBq/mL (4 – 100 mCi/mL) |
| Route of Administration | IV Injection |
| Rx/OTC Dispensed | Rx |
| Applicant | Zionexa US Corp (11650 Olio Road-Suite 1000-163, Fishers, IN 43037 |
| US agent, if applicable | N/A |

| SUBMISSION(S) REVIEWED (seq. no.) | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| Original | February 28, 2019 | CMC Product Quality; Microbiological Product Quality; Manufacturing facilities |

Quality Review Team

| DISCIPLINE | PRIMARY REVIEWER | SECONDARY REVIEWER |
|---|---|---|
| Drug Substance | Soumya Mitra | Donna Christner |
| Drug Product | Dhanalakshmi Kasi | Danae Christodoulou |
| Process | Dhanalakshmi Kasi | Danae Christodoulou |
| Microbiology | Xia Xu | Nandini Bhattacharya |
| Facility | Krishna Ghosh | Vidya Pai |
| Biopharmaceutics | Hansong Chen | Topash Ghosh |
| Environmental | Dhanalakshmi Kasi | Danae Christodoulou |
| RBPM | Anika Lslmsndingh | N/A |
| Application Technical Lead | Eldon E. Leutzinger | N/A |

Quality Review Data Sheet

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF #[1] | Type | Holder | Item Referenced | Status | Date Review Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | V | | (b) (4) | (2) | (2) | (2) |
| | V | | | Adequate | (3) | N/A |
| | V | | | Adequate | (3) | N/A |
| | III | | | Adequate | (3) | N/A |
| | IV | | | Adequate | (3) | N/A |

(1) Letters of authorization from the holder of the DMF's are submitted with the NDA.
(2) DMF in Biologics.
(3) Adequacy for use in NDA product assessed in drug product review.

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

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| N/A | | |

## 2. CONSULTS

| DISCIPLINE | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| N/A | | | |

# Executive Summary

## I. Overall Recommendation on Approvability

OPQ recommends [**APPROVAL**] of NDA [212155] for commercialization of [Fluoroestradiol F 18 Injection, 148 MBq/mL to 3700 MBq/mL (4 mCi/mL to 100 mCi/mL) @ End of Synthesis] with an expiration dating period of [10] hours:

- With adequate resolution of all CMC issues identified, 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 (b) (4) ).

- The proposed labeling and labels [have] adequate information to meet the regulatory requirements.

## II. Product Quality Review Context

**Indication and Intended Population** - Fluoroestradiol F 18 Injection is a sterile solution of **[$^{18}$F]16α-fluoro-3,17β-diol-estratriene-1,3,5(10)** for use with positron emission tomography (PET imaging) in characterizing the estrogen receptor (ER) status (b) (4) breast cancer. The parent to FES, estradiol (or estradiol-17β) is a naturally occurring steroid and is lipophilic, generally present in slightly higher concentration in tissues with higher fat content. The history of investigational use of this drug dates from the mid-1980's, and the drug had received approval for marketing in France in 2016. Concurrent with the continuing investigational use of the drug, therapeutic options for treatment of breast cancer have been increasing, giving impetus for development of an imaging drug to evaluate receptor status of cancer lesions.

**Regulatory Context - Designation of Drug Substance**:
The active ingredient in Fluoroestradiol F 18 Injection is that substance which is radioactive, **[$^{18}$F]16α-fluoro-3,17β-diol-estratriene-1,3,5(10)** (21 CFR 310.3 (n)), interpreted as the drug substance, meaning that it *"is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, …of disease…"* (21 CFR 314.3)]. The science is clear here. Creation of the image to reveal diagnostic information to address the indication is driven by both biodistribution of the chemical system in [$^{18}$F]16α-fluoro-3,17β-diol-estratriene-1,3,5(10), with similarity to estradiol, and the radioactive emissions from the radionuclide ($^{18}$F).

(**Principle**). Radiolabeling with introduction of $^{18}$F for imaging creates a '**structural mimic**' ($^{18}$F for H), preserving the pharmacophore properties of base substance Estradiol (by virtue of the physicochemical properties of F, minimizing any adverse effect of replacement of H by F).

**Regulatory Context - Regulatory Status of the Precursor**:
(b) (4) That creates additional consequences (in the analytical context) that impacts strength and specific activity determinations, intensifying the criticality of the Precursor. **These circumstances raise the controls for the Precursor to the level of scrutiny as for an API**.

**Regulatory Context** – **Comparability Protocol (CP)**:

(b) (4)

**Product Profile and Critical Quality Attributes (CQA's)**:
Fluoroestradiol F 18 Injection is a sterile aqueous solution of **[$^{18}$F]16α-fluoro-3,17β-diol-estratriene-1,3,5(10)** with sodium ascorbate (b) (4), sodium chloride (b) (4) and ethanol (b) (4) It is near isotonic with osmolality of 340 mOsm, and pH in the range of 4.5 – (b) (4). Flurorestradiol F 18 Injection is supplied in 40 mL in a 50 mL multidose glass vial at a strength of 148 – 3700 MBq/mL (4 – 100 mCi/mL) at end of synthesis.

Fluoroestradiol F 18 Injection was developed at Zionexa, France and the commercial manufacturing site is (b) (4) Batch sizes of (b) (4) mCi are manufactured at (b) (4) while the larger size ((b) (4) mCi) is manufactured at Zionexa.

Unique with Fluorestradiol F 18 Injection is the (b) (4) Radiochemical Purity CQA and the integrity of the (b) (4). It is also in large measure a factor that keeps down the number and extent of side-reactions, but also adds challenge to the analytical quality controls for low-level impurities.

**Areas of Unique Focus**:

- **Radiolabeling Chemistry**

(b) (4)

- **Ancillary Areas - Control of Materials**

(b) (4)

(b) (4)

- **Analytical Methods**

The importance of analytical methods rests with the expectation that they will produce credible and trustworthy results, and for quantitative methods will produce numerical values close to the true values within an acceptable level of accuracy, depending on the intended use of the results. This becomes critical for low-level impurities analysis, as they are for Fluoroestradiol F 18 Injection (5 µg/dose).

(**Analytical Methods Validation**). The intention of methods validation is to establish the foregoing expectations, given that during methods development the limits and operation boundaries have been well-defined. Again, this becomes critical in the case for analytical methods that need to be capable of delivering accurate and reliable results for low level impurities, as here for Fluoroestridiol F 18 Injection where the impurity level is of the order of 5 µg/dose.

## III. Summary of Quality Assessments

The following are from the Mid-Cycle Information Requests (8/08/2019).

**DRUG SUBSTANCE (i.e., (b) (4) PRECUSOR)[1,2]**

See sections (1) of Executive Summary (page 5) for Regulatory Context defining Drug Substance and Precursor. This section summarizes those issues as identified by the drug substance reviewer (Soumya Mitra, Ph.D.).

(b) (4)

Aside of a single ancillary issue regards the bulk container (**COMMENT #1 - Resolved**), most important are those issue regarding the integrity of the precursor. The maintenance of integrity of the precursor is paramount, because of its pivotal role in assuring that the intended drug substance molecule is the outcome of radiolabeling. The needed assurance for a well-characterized precursor is intensified by the (b) (4) That a **Reference Standard** for the precursor is in place is essential to quality control of the precursor. But there is little information provided on that reference standard (**Comment- #2**) - **Resolved**. Its **Impurity Profile** is critical for two reasons. Firstly (1) an unwanted impurity may be carried into the final product and thence may confound the (b) (4). Secondly (2) an impurity may interfere with radiolabeling. Based on these justifications, there are two known impurities (NMT (b) (4) %) the names of which need to be designated and categorized as "specified impurities." The (b) (4) % limit is for each impurity. Since these two impurities appear to be the only impurities of significance, (b) (4) % for each brings the total to (b) (4) %. As well, there is need to tighten limits the for unspecified impurities to NMT (b) (4) % (**Comment # 3**) - **Resolved**. An additional issue was identified (Martin

Haber, Ph.D. of review team), necessitating adding to the precursor specifications an acceptance limit and a specification for assay for the content of the precursor (**Comment # Additional**). Also conveyed to the applicant in these regards is that the same HPLC procedure used for the determination of impurity may be used for these additional specifications – **Resolved**.

**DRUG PRODUCT**

This section summarizes those issues as identified by the drug product reviewer (Dhana Kasi).

The issues identified for the drug product can be collected into 4 major categories (Excipients, (b) (4) and other Ancillary Items, Analytical Methods/Specifications, Analytical Methods Validation and Stability). As well as (b) (4), the Ancillary items include, e.g., container-closure, which was addressed with information that was missing in the original submission. Within the category of ***Specifications***, concerns are raised regards pH (wideness), absence of SST's for the critical analytical methods (RCID, RCP and chemical purity), and the characterization of impurities (**Comment #2, #6, #7**) - **Resolved**. The ***Instability*** of a radiopharmaceutical is largely a result of (b) (4) In these regards, there was lack of information to support stability at both lower and higher strengths throughout the proposed shelf-life (**Comment #9**) - **Resolved**. Based on the stability test results, an expiration date is set at 10 hours storage at room temperature and @ EOS.

There is a Post-Approval Stability Protocol and Commitment to put a minimum of one batch of Fluoroestradiol F 18 Injection on stability, with the entire batch stored inverted at $22.5^0$C ± $7.5^0$C and sampled at 10 and 12 hours post EOS. Testing will be in accordance to the established specifications.

***Excipients and*** (b) (4) as well as ***Analytical Methods/Validation*** engender greater discussion, as radiochemical synthesis is unique within the manufacturing framework, and subject to a host of special problems and considerations not possessed by the manufacture of conventional drug products.

There are outstanding issues identified in the Manufacturing Process, principally lack of information ranging across the critical process parameters, (b) (4) to the absence of defined procedures in quality assurance of batch records (**COMMENT #8**) - **Resolved**

**Excipients and** (b) (4):

Although the degree of integrity of (b) (4) is important in all manufacturing, radiochemical synthesis is especially sensitive to its effects. (b) (4) for the final

product, and puts stress on RCP testing (by HPLC) along with choice of a suitable acceptance criterion. Although not primary contributor to product quality, the ancillary item (container closure) for the drug product is nevertheless important for several reasons that includes the chemical composition of the glass and other container-closure attributes that could affect final product purity and sterility (**COMMENT #10**) – **Resolved**.

Regards **excipients**, obviously the degree of their integrity bears directly on the state of the chemical purity of the final product. **In the original submission, it was not clear that they have in place adequate procedures for quality control of these materials** (b) (4) **excipients), and this bears on the adequacy of the controls on the manufacturing process**, the basis of **Comment #1 - Resolved**. Since this is a PET drug, 212.40 applies here, i.e., "instead of full testing, a certificate of analysis (COA) may be accepted provided the PET center establishes the reliability of test results," and "use qualified vendors." Historically, a number of work-arounds have been considered, one of which includes limited testing with COA. But no agreement could be made as to what is a suitable test to use and became contentious among PET producers. Ultimately, it comes down to "qualification" interpreted as the outcome of a PET production with a subject raw material and used as a test for its acceptability – the essential gist of 212.40. Each PET center is left with the responsibility of this qualification.

**Analytical Methods**:
There are a variety of problems in the analytical methods, that include (1) lack of procedural detail (method instructions – radiochemical purity, strength, etc.), (2) lack of system suitability testing acceptance criteria, (3) lack of Quality Assurance of batch records and associated analytical raw data, as well as general aspects of analytical quality control practice ('housekeeping items,' e.g., lack of control of (b) (4) ), all issues within **COMMENT #6** – **Resolved**.

**Methods Validation**:
The original methods validation (in France), where the method was developed, is not made available (original submission), thus rendering an **incomplete methods validation** (**COMMENT #3, #4**). Hence, this inherently handicaps the evaluation of (b) (4) **Report of HPLC Method Transfer** document (Appendix 3.2.P.5.3), which contains the **verification results** of the transfer of this method from its origination to the (b) (4). A response from the applicant (8/08/2019) provides a completely revised Methods Validation section (Zionexa). Zionexa indicated that there is a slight difference between the French and US HPLC method; hence, the method was fully validated at the (b) (4) and included specificity, accuracy, precision (repeatability, intermediate), linearity, range, LOD and LOQ, and robustness. Based on the information provided and the evaluations from the primary reviewer and ATL, Comments # 3 and #4 are considered **resolved with regarding the methods validation performed at the site where the HPLC method was developed and full validation performed at the** (b) (4) **to address a what is described as a slight difference between the French and US method**.

The **Limit of Quantitation** is often overlooked for radiopharmaceuticals, more emphasis being placed on Limit of Detection (carrier mass, non-radioactive impurities). Yet, because the acceptance criteria for impurities is numerical, the said method must be capable of quantitating these levels and especially the level of **impurities that exceed the detection limit**, elevating the criticality of this validation characteristic. The lack of this capability in their HPLC method for impurities is corrected in the revised methods validation. Including the Limit of Quantitation, the revised methods validation corrects all the analytical method validation issues that were identified in the primary review of the application.

More specifically, the revised HPLC methods validation closely follows the July 2015 FDA Draft of Analytical Procedures and Methods validation for Drugs and Biologics in reference to the ancillary areas that outlines the *Principle/Scope*,….,*Standards Control Solution Preparation*,…., etc., fundamental to establishing the logic of its execution. It incorporates the panel of validation characteristics (listed in 2015 FDA Draft) and procedures for their determination (Q2(R1)). **Its relevancy for the HPLC method is demonstrated with the quantitative validation characteristics fully covering the concentration range ( (b) (4) µg/mL), consistent with the specifications and the dose amounts at the 10 mL maximum dose volume**. The applicant follows sound principles and validation procedures for **Precision** (repeatability, intermediate, measured in terms of %RSD of replicates), **Accuracy** (%Recovery), **Linearity** ($R^2$ and Y-intercept) and **Robustness** (%RSD of replicates) and that of **Specificity** (Resolution, $R_S > 1.5$; Stability of Retention Times and Peak Areas, measured as % RSD, ≤3% RT, ≤5% Area). **The raw data provided in the revised methods validation for precision, accuracy, linearity, robustness and specificity were analyzed independently (by ATL) and the results/conclusions confirmed to be reasonably consistent with those by the applicant.**

Although all these validation characteristics are important, **LOD and LOQ stands out with particular importance here, because they are critical to the HPLC method's capability of quantitating low-levels of impurities in Fluoroestradiol F 18 Injection (as noted in the drug product review by Dhana Kasi)**. The issues with regard to these validation characteristics have been satisfactorily addressed in the revised methods validation. However, what remains as particularly noticeable is the rather simplistic and peculiar form of their equation, **3((h/2)C)/H**, for calculating LOD from Signal to Noise data from the raw chromatograms, and its associated form for LOQ (replacing the factor 3 with 10) – see NOTES, in the context of the results in Tables 18/19. The noise level is h/2, measured from the midpoint of the noise bandwidth, and hence the signal is taken as 2H (European Pharmacopeia). Through rearrangement, 3((h/2)C)/H becomes **3C/(2H/h)** which translates to **3C/(S/N)**, which shows some semblance to 3.3σ/Slope of the calibration curve method for LOD, except that S/N (a measure of detectability) and Slope (a measure of sensitivity) are fundamentally different concepts. And, σ (standard deviation) is not visibly seen in the equation. Their equation, 3((h/2)C)/H, is not in Q2(R1). Nor does it appear to be in the analytical chemistry literature. Yet, there is an aura around this equation suggesting that (S/N)

acts as a factor converting the variable C into some concentration of the analyte that when coupled with a statistical quantity yields the 'minimum concentration' for which the analyte can be reliably detected, the basis for the impression that 'their version' of the Signal to Noise method is related to the calibration curve method for Limit of Detection, and is the basis of the aforementioned semblance (see NOTES).

**NOTES (by ATL)**:
It does appear that they follow a version of the Signal to Noise method described in Q2(R1), where *"measured signals from samples with known low concentrations of analyte are compared with blank samples, establishing a minimum concentration for which the analyte can be reliably detected*." But, the equation, **3((h/2)C)/H**, or **3C/(S/N)**, has an "incomplete appearance," not intelligible at face value, when compared with other methods for Limit of Detection, a case in point (as already mentioned) being the calibration curve method for which the equation is 3.3σ/S, where S is the slope. Firstly (1), the factor 3 in 3C/(S/N) suggests that it is there for the purpose of associating with the calculation a level of statistical significance so that it refers to a concentration that can be 'reliably detected.' Yet, it is not obvious that the required σ is contained in 3C/(S/N) that would make this happen. Secondly (2), and what characterizes their version of the method in Q2(R1) is that **the concentration denoted as C is not the 'minimum concentration' spoken of in Q2(R1), but rather some nondescript value obtained in experiments serving supposedly as a 'suitable' figure from which to derive an estimate of LOD.**

Despite these peculiar characteristics, and based on intuition, the author of this Executive Summary shows in the following NOTES that their equation is meaningful and applicable to the method of Signal to Noise.

Their equation, 3((h/2)C)/H, for calculating Limit of Detection can be rigorously derived. The **first (1) key** to making sense of 3((h/2)C)/H lies in the realization that the statement of method principle in Q2(R1) is quite general, leaving out details of how to carry out that principle. In this context, **the supposition is that C in 3((h/2)C)/H is some value of analyte concentration arrived at through their version of the method principle,** surmised to be serial dilution of a starting concentration $x_j$, or similar process. In the serial dilution format, [$\mathbf{x_0}$,.,C,…..$x_j$], $\mathbf{x_0}$ can arbitrarily be denoted as an 'absolute' value of the Limit of Detection, and C as some variable of concentration the value of which can in this context be interpreted as a 'guess' at $x_0$ (by serial dilution and perhaps with assistance from experience with the analytical method). Although $C \neq x_0$, it nevertheless would be interpreted to fall closely within the immediate neighborhood of $x_0$, i.e., $C = \xi x_0$ with the condition that ξ must be approaching 1 so that $C - \xi x_0 \rightarrow 0$. So, something must be done to C to convert it to $x_0$, i.e., $(1/\xi)C = x_0$, where $1/\xi = 3/(S/N)$. As $\xi = 3/(S/N) \rightarrow 1$, $C \rightarrow x_0$. This means that when 3/(S/N) = 1, the experimentally determined concentration (C) in the serial dilution would hit $x_0$ exactly. If that result could be attained, it would mean there is 100% probability of detecting the analyte at that concentration (C) with their analytical method. The axis of analyte concentrations [$\mathbf{x_0}$,.,C,…..$x_j$] containing their calculated result, 3C/(S/N), can be mapped onto a probability distribution (allowed

through intermediate form, $3\sigma_b/(y_C/C)$, reference to next paragraph), and as such is in terms of units of σ (standard deviation). Their result, 3C/(S/N), falls within this axis in an interval associated with a given probability of containing $x_0$, thus aligning with the meaning of 'reliably detected' in Q2(R1).

Building onto the aforementioned, the **second (2)** key is the realization **that σ must enter the picture during the derivation of 3C/(S/N), becoming internalized, and thenceforth lives in the equation as a ghost**. Now, the raw signal ($y_j$') from each concentration is comprised of the analyte signal and noise (background). On subtraction of background, one gets [$\mathbf{y_0}$,.,$y_C$,…$y_j$], where $y_0 = y_0' - y_b = 3\sigma_b$, the signal from $x_0$ (definition of Limit of Detection, *Statistics for Analytical Chemistry, J.C.Miller and J.N.Miller, 3rd edition 1993, Ellis Horwood Limited, , New York, etc.*). By application of Beer's Law, the result becomes $x_0 / C = 3\sigma_b / y_C$ (UV detection at 280 nm). From the Beer's Law result, $x_0 = (3\sigma_b)C/y_C$, thus pairing up $\sigma_b$ with the factor 3, revealing how standard deviation enters this initial form of the developing equation. But, on rearrangement, it becomes $x_0 = 3C(\sigma_b/y_C) = 3C / (y_C/\sigma_b)$. From the published literature from NIST (Statistical Engineering Division), $(y_C/\sigma_b)$ is one of several **statistical definitions of S/N**. Hence, $x_0 = 3C/(y_C/\sigma_b) = 3C/(S/N)$, showing how $\sigma_b$ is internalized (i.e., hiding away in the equation). Estimating S/N with 2H/h, the result becomes 3C/(2H/h), or **3((h/2)C)/H**, their equation for calculating Limit of Detection from S/N data.

On rearrangement of the first form in the string [$x_0 = (3\sigma_b)C/y_C = 3C(\sigma_b/y_C) = 3C/(y_C/\sigma_b)$], the result becomes $(3\sigma_b)C/y_C = 3\sigma_b/(y_C/C)$. The fraction $(y_C/C)$ is the amount of change in the response ($y_C$) per change in analyte concentration. As $(y_C/C)$ is a measure of sensitivity, this intermediate form, $3\sigma_b/(y_C/C)$, relates to 3.3σ/Slope. This means that there is a common logic-thread relating the equations for the Signal to Noise and Calibration curve methods (in fact, relates both methods), as the impression conveys, providing additional support of the validity of 3((h/2)C)/H.

This framework with the string starting from Beer's Law [$x_0 = (3\sigma_b)C/y_C = 3\sigma_b/(y_C/C) = 3C(\sigma_b/y_C) = 3C/(y_C/\sigma_b) = 3C/(S/N) = 3C/(2H/h) = 3((h/2)C)/H$] places their equation, 3((h/2)C)/H on a sound scientific basis, verifying its relevance for calculating an estimate of the Limit of Detection from S/N data and the validity of the LOD results in Tables 18/19. Replacing $y_0 = 3\sigma_b$ by $y_0 = 10\sigma_b$ in the derivation gives an estimate of the LOQ.

**Comparability Protocol (CP):**

(b) (4)

These changes are the following, any one of which will necessitate submission of a Prior Approval Supplement (PAS):

- (b) (4)

**Zionexa has agreed to this and their response is acceptable by FDA**.

(b) (4)

(b) (4)

**Integrity of the Radiolabeling Chemistry**:

(b) (4)

Because of this criticality, the following is provided in NOTES.

**NOTES (by ATL)**:

(b) (4)

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(b) (4)

(b) (4) **With this resting on a sound foundation of theoretical and physical organic chemistry, it strengthens the principles upon which the applicant's CMC plan is based, confidence in the batch results and the expectation of their perpetuation in future production batches.**

**Product Labeling**:
During review of the drug product labeling (Dhana Kasi), the vial labels were found in need of revisions. This included an expiration date and time, storage condition, drug product composition, and total volume for the multi dose vial, and the statement, "do not use if it is cloudy or contains (b) (4) particulate matter" in the vial label (**LABELING COMMENT**) – **Resolved**.

**Microbiology:**
In summary, the drug product is (b) (4) . From the Microbiology review, all issues have been adequately addressed, and the final decision is an overall adequate (3/17/2020, Xia Xu, Ph.D.).

**Biopharmaceutics:**
From the Biopharmaceutics review (Hansong Chen, Ph.D.), "the Biopharmaceutics review focuses on the side-by-side comparison between the proposed product and the ones in the literature and assesses whether the bio-bridge between them is sufficient." This determination for Fluoroestradiol F 18 Injection is adequate (3/13/2020).

**Facility Inspections**:
There are two facilities associated with this NDA.

- (b) (4) – responsible for the manufacture of Fluoroestradiol F 18 Injection, a well as its packaging, and controls.
- (b) (4) – ISO certified facility responsible for (b) (4)

The (b) (4) is deemed acceptable by PAI inspection and review of IR response to FDA 483 (3/11/2020). (b) (4) (manufacturer of precursor, packaging, release and stability testing is determined to be accepted by file review. In accordance to the facilities review (3/11/2020), **"a post-approval inspection will be recommended to ensure that all process and analytical assay related corrective actions have been completed adequately."**

## IV. Final Analysis of Product Quality Review Issues

There are no outstanding issues remaining from the standpoint of CMC (precursor to the drug substance, drug product, microbiology, facilities). (b) (4)

(b) (4)

[redacted]

## V. Summary Basis for Product Quality Recommendation

The applicant has provided adequate information to ensure the identity, strength, and purity of the proposed drug product. Together with the Comparability Protocol, no outstanding issues remain.

## VI. Lifecycle Considerations

(b) (4)

[redacted]

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***Labeling Review:***

Vial label (immediate container)


Lead shield (canister) label (external container)


**Reviewer's Assessment: Adequate**

The container and lead shield label were reviewed. The container label lacked expiration date and time, storage condition, drug product composition, total volume, multi dose vial and "do not use if it is cloudy or it contains (b) (4) particulate matter".

**Information Request Sent on 11 Mar 2020:**

Include expiration date and time, storage condition, drug product composition, total volume, multi dose vial and "do not use if it is cloudy or it contains (b) (4) particulate matter" in the vial label.

**Reviewer's Evaluation:** The Applicant included all the suggestions provided in the vial label. Acceptable.

**Package Insert Information:**

## 3 DOSAGE FORMS AND STRENGTHS

Injection: clear, colorless solution in a multiple-dose vial containing 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) of fluoroestradiol F 18 at end of synthesis.

## 11 DESCRIPTION

### 11.1 Chemical Characteristics

CERIANNA contains fluoroestradiol fluorine 18 (F 18), a synthetic estrogen analog. Chemically, fluoroestradiol F 18 is [18F]16α-fluoro-3,17β-diol-estratriene-1,3,5(10). The molecular weight is 289.37, and the structural formula is:

CERIANNA is a sterile, clear, colorless solution for intravenous injection, with an osmolarity of 340 mOsm. Its pH ranges between 4.5 to (b) (4). The composition of the final product in 40 mL solution is fluoroestradiol no more than 5 µg, fluoroestradiol F 18 148 MBq/mL to 3,700 MBq/mL (4-100 mCi/mL), sodium ascorbate 0.44% w/v in sodium chloride 0.9% w/v, and ethanol no more than 3.2% w/v.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

CERIANNA is supplied in a 50 mL multiple-dose glass vial (NDC# 72874-001-01) containing a clear, colorless injection solution at a strength of 148 MBq/mL to 3,700 MBq/mL (4 mCi/mL to 100 mCi/mL) fluoroestradiol F 18 at the end of synthesis. Each vial contains multiple doses and is enclosed in a shield container to minimize external radiation exposure.

### 16.2 Storage and Handling

**Storage**

Store CERIANNA at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Store CERIANNA upright in the original container with radiation shielding. The expiration date and time are provided on the container label. Use CERIANNA within 10 hours from the time of the end of synthesis.

Dhanalakshmi Kasi

Digitally signed by Dhanalakshmi Kasi
Date: 3/23/2020 09:48:36AM
GUID: 53150dea000054615f30e13bde0d487c

Eldon Leutzinger

Digitally signed by Eldon Leutzinger
Date: 3/23/2020 10:11:56AM
GUID: 508da7210002a0781943eff6cc724d1f

Danae Christodoulou

Digitally signed by Danae Christodoulou
Date: 3/23/2020 10:06:58AM
GUID: 5050dd27000012a4c69bfc70b47660b7

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# CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

| | |
|---|---|
| **Product Information** | (b) (4) ([18F]-Fluorestradiol Injection) |
| **NDA Number** | 212155 |
| **Assessment Cycle Number** | 01 |
| **Drug Product Name/ Strength** | (b) (4) ([18F]-Fluorestradiol Injection) |
| **Route of Administration** | IV injection |
| **Applicant Name** | Zionexa US Corporation |
| **Therapeutic Classification/ OND Division** | Medical imaging/DMIP |
| **RLD/RS Number** | N/A |
| **Proposed Indication** | (b) (4) |

***Assessment Recommendation:*** **Adequate**

***Assessment Summary:***

Zionexa US Corporation developed (b) (4) ([18F]-Fluorestradiol Injection) and totally relied on the findings on efficacy and safety reported in the literatures and submitted the application under NDA 212155 to seek approval from the Agency through 505(b)(2) regulatory pathways on 2/27/2019. The proposed indication of the proposed PET Imaging agent is for (b) (4)

(b) (4)

The Biopharmaceutics review focuses on the side-by-side comparison between the proposed product and the ones reported in the literatures and assesses whether the biobridge between them are sufficient.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA 212155 for (b) (4) ([18F]-Fluorestradiol Injection) is **adequate** for approval.

**List Submissions being assessed (table):**

| Document(s) Assessed | Date Received |
|---|---|
| eCTD-0004/original submission | 2/27/2019 |
| eCTD-0008/Response to biopharmaceutics IR | 7/5/2019 |
| eCTD-0012/Response to biopharmaceutics IR | 9/6/2019 |

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

**Concise Description of Outstanding Issues (List bullet points with key information and update as needed):** None.

## A. BRIDGING OF FORMULATIONS

**Assessment: *{Adequate }***

Because the Applicant totally rely on the findings of the literatures on efficacy and safety, the Applicant should bridge the commercial formulation and the ones reported in the references. Here are some importance references reporting the clinical studies of (b) (4) ([18F]-Fluorestradiol Injection), and the Applicant took the study results as evidence of safety and efficacy:

Table 1. The references cited by the Applicant

| Clinical study category | References |
|---|---|
| PK study | Tewson TJ et al. Nucl Med Biol 26;8:905–913, 1999.<br>Mankoff DA et al. Nucl Med Biol. 24(4):341-8, 1997<br>Mankoff DA et al. Semin Radiat Oncol. 2001 Jan;11(1):16-27. |
| Pivotal efficacy and safety study | Peterson et al. Mol Imaging Biol. 2014; 16(3): 431–440.<br>Venema at al. J Nucl Med 2017; 58:1906–1912.<br>Chae et al. Lancet Oncol 2019; 20:546-55. |

As requested, the Applicant provided a side-by-side comparison between the proposed product and the ones reported in the literatures, which is listed in the table below:

Table 2. side-by-side comparison between the commercial formulation and the ones reported in the references

| Drug product | API | Specific activity | NaCl | Ethanol | Other excipients |
|---|---|---|---|---|---|
| The proposed drug product | 16α-[18F] fluoro-17β-estradiol | > (b) (4) Ci/μmol EOS | 0.9% (W/V) | NMT 3.2% (w/v) | Sodium Ascorbate 0.44% (b) (4) % (w/v) |
| Mankoff DA 1997 | 16α-[18F] fluoro-17β-estradiol | 1 Ci/μmol | | Below 10% | Phosphate-buffered saline Concentration Not available |
| Mankoff DA 2001 | 16α-[18F] fluoro-17β-estradiol | 1–2 Ci/μmol | Not available | Below 10% | |
| Tewson 1999 Drug | 16α-[18F] fluoro-17β-estradiol | > 1 Ci/μmol | | 2-10% | |
| Peterson et al. 2014 | 16α-[18F] fluoro-17β-estradiol | 2.5 Ci/μmol at injection | | Not more than 15% | |
| Venema et al. 2017 | 16α-[18F] fluoro-17β-estradiol | Not available | | | Suitable solvent not available |
| Chae et al. 2019 | 16α-[18F] fluoro-17β-estradiol | 1.5 Ci/μmol | 0.8% | Not more than 10% | Ascorbic acid 20 mg/mL |

**Reviewer's comments:**

*Here is the summary of the side-by-side comparison between the commercial formulation and the ones reported in the references:*

- *The Applicant did not have all information about the formulations reported in the literatures.*
- *The formulations reported in the references do not have the same excipients as that of the commercial one.*
- *In all cases, the radiochemical purity has been assessed to be greater or equal to 95.0%.*
- *Lancet Oncol 2019; 20:546-55 is the most important reference for the medical team to consider for efficacy and safety.*

*The proposed commercial formulation is not exactly same as the literature reported products. However, it may be possible to establish a biobridge between the proposed product and the literature reported products with adequate justification as per 21 CFR 320.24(b)(6) due to the following reasons:*

- *The specific activity is one of the key factors for medical imaging agent. Specific activity refers to the amount of radiolabeled mass in a sample, often expressed as Ci/mmol (Ci/mol) or Ci/mg. The commercial product has higher specific activity than the reported drug products. Specifically, the proposed drug product has specific activity of >* (b) (4) *Ci/μmol, and the specific activity of the formulation reported in Lancet Oncol 2019; 20:546-55 is 1.5 Ci/μmol.*
- *Both the proposed drug product and the formulations reported in the references are aqueous based solution and are administered for IV injection.*
- *Although they have different excipients, those differences are not expected to affect in vivo performance.*

*Please note that it may not be sufficient for approval without additional safety/efficacy studies. Decision in these regards needs to be determined by Clinical and other disciplines.*

## B. BIOWAIVER REQUEST

**Assessment: *{Adequate }***

The Applicant requested the waiver of in vivo bioavailability for the proposed Fluoroestadiol $F^{18}$ Injection. By citing 21 CFR 320.22(b)(1)(i) and (ii), the Applicant stated that the proposed drug product is an IV injection solution and its bioavailability is considered self-evident.

In Module 2.7.2.1.1 Pharmacokinetics of [18F]Fluoroestradiol, the Applicant reported that the pharmacokinetics of FES is similar to that of the intravenous estradiol reported in the literature. The Applicant pointed out that the following article reported the PK parameters of [18F]Fluoroestradiol. However, the Applicant did not clarify if the proposed drug product and the drug reported in the reference have the same components and composition.

Reference:

Tewson TJ, Mankoff DA, Peterson LM, Woo I, Petra P. Interactions of 16alpha-[18F]-fluoroestradiol (FES) with sex steroid binding protein (SBP). Nucl Med Biol. 1999;26(8):905-13.

**Reviewer's comment**

*This Reviewer communicated with the Clinical Pharmacology Reviewer regarding the biowaiver. It was concluded that the PK data of [18F]-Fluorestradiol are essential for the package insert. The Clinical Pharmacology Reviewer would be sending an IR to*

*request more about distribution, identity, and efficacy (imaging related) of metabolites and excretion of parent and any imaging related active metabolite.*

*Overall, the proposed commercial formulation is not exactly same as the literature reported products. However, based on the provided information and justifications described below, a biobridge between the proposed product and the literature reported products has been established as per 21 CFR 320.24(b)(6):*

- *Both the commercial product and reported drug products are for IV injection.*
- *The differences in excipients are not expected to affect drug disposition.*
- *Based on the overall supportive information, it is expected that the bioavailability of the proposed drug and the ones reported in the literatures are similar.*

**Appendix I. Information request**

**IR 1**

On June 10, 2019, the first Biopharmaceutics IR was sent to the Applicant:

In Module 2.7.2.1.1 Pharmacokinetics of [18F]Fluoroestradiol, you cited several articles to report the PK performance of [18F]Fluoroestradiol. However, you did not clarify if the proposed drug product and the drug product reported in the references have the same component and composition.

Submit a side-by-side comparative table of the formulation reported in the references and your proposed drug product formulation to the Agency for review. If there exists difference/s, explain the impact of them on the in vivo performance of [18F]Fluoroestradiol.

**IR 2**

On August 27, 2019, the second Biopharmaceutics IR was sent to the Applicant:

Submit a side-by-side comparison between the formulations reported in the following references and your proposed drug product formulation to the Agency for review. If there exists difference/s, explain their impact on the in vivo performance of [18F] Fluoroestradiol.
References:

Peterson et al. *Mol Imaging Biol*. 2014 June; 16(3): 431–440.

Venema et al. *J Nucl Med* 2017; 58:1906–1912.

Chae et al. *Lancet Oncol* 2019; 20:546-55.

## R. REGIONAL INFORMATION

Comparability Protocols

**Assessment: *{Adequate/Inadequate}***

Post-Approval Commitments

**Assessment: *{Adequate/Inadequate}***

Lifecycle Management Considerations

## BIOPHARMACEUTICS LIST OF DEFICIENCIES

*Primary Biopharmaceutics Assessor's Name and Date:*

*Hansong Chen, PharmD, Ph.D.*
*OPQ/ONDP/BII*
*March 13, 2020*

*Secondary Assessor Name and Date (and Secondary Summary, as needed):*

*Tapash Ghosh, Ph.D.*
*OPQ/ONDP/BII*

Hansong Chen

Digitally signed by Hansong Chen
Date: 3/23/2020 02:53:34PM
GUID: 525d7d660003845a197a2e1682433d0d

Tapash Ghosh

Digitally signed by Tapash Ghosh
Date: 3/23/2020 02:56:30PM
GUID: 508da7230002a2433ddcef616ca190df

# CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

| | |
|---|---|
| **Product Information** | Fluorestradiol F 18 Injection is a radioactive diagnostic agent for positron emission tomography (PET) imaging. It is indicated for characterization of estrogen receptor status (b) (4) breast cancer. |
| **NDA Number** | 212155 |
| **Assessment Cycle Number** | 01 |
| **Drug Product Name/ Strength** | Fluoroestradiol F 18 Injection, 4-100 mCi/mL @ EOS |
| **Route of Administration** | Intravenous |
| **Applicant Name** | Zionexa-US Corporation (formerly known as Cyclopharma-US Corporation)<br>205 E 42nd Street, c/o WeWork, New York NY 10017 |
| **Therapeutic Classification/ OND Division** | Radioactive diagnostic agent for PET imaging |
| **Manufacturing Site** | (b) (4) |
| **Method of Sterilization** | (b) (4) |

***Assessment Recommendation:*** **Adequate**

***Assessment Summary:*** The subject PET drug product is (b) (4) (b) (4) container closure system.

**List Submissions being assessed (table):**

| Document(s) Assessed | Date Received |
|---|---|
| Supporting document # 4 (Original) | 02/27/2019 |
| Supporting document # 8 (Amendment) | 05/03/2019 |
| Supporting document # 15 (Amendment) | 09/30/2019 |
| Supporting document # 23 (Amendment) | 02/03/2020 |
| Supporting document # 26 (Amendment) | 03/11/2020 |

**Highlight Key Issues from Last Cycle and Their Resolution:** None

**Remarks:** eCTD/Global submit review. This is a 505(b)(2) submission. Fluoroestradiol F 18 Injection has been approved in France and is distributed commercially under the proprietary name of EstroTep. Zionexa US Corporation is a subsidiary of Zionexa headquartered in France.

The Agency issued the Information Request to the applicant on 04/10/2019, 08/08/2019 (Mid-Cycle communication), and 12/10/2019. The applicant's Responses dated 05/03/2019, 09/30/2019, and 02/03/2020 are incorporated in this review.

**Concise Description of Outstanding Issues**
**(List bullet points with key information and update as needed):** None

**Supporting Documents:** N/A

**List Number of Comparability Protocols:** 1

## S DRUG SUBSTANCE

The drug substance, Fluoroestradiol F 18, is (b) (4) (b) (4) (b) (4) The drug substance is not isolated or in-process tested. This drug substance section is therefore not reviewed for sterilization process validation. The excipients and (b) (4) are tested for bacterial endotoxins and microbial limits or sterility with the following acceptance criteria (3.2.P.3.2 Specifications, CofA – Batch (b) (4) .pdf):

| Excipient (b) (4) | Supplier | Endotoxin Limit | Microbial Limits | Sterility |
|---|---|---|---|---|
| (b) (4) | | | | |

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## *2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1*

### *2.A. Prescribing Information*

Storage temperature: Controlled room temperature 20-25ºC (68-77ºF)
Route of administration: Intravenous
Container: Multiple dose

- Post-dilution/constitution hold time

The subject drug product is used directly without any further dilution or reconstitution. However, the package insert also indicates that the Fluorestradiol F 18 may be diluted with Sodium Chloride Injection, 0.9%. The post-dilution storage condition is not specified. The reviewer considers the diluted PET drug product is to be administered immediately.

**Assessment: *{Adequate}***

Post-Approval Commitments – See P.8.2

**MICROBIOLOGY LIST OF DEFICIENCIES**

**None**

***Primary Microbiology Assessor Name and Date:***
Xia Xu, Ph.D. 03/17/2020
***Secondary Assessor Name and Date (and Secondary Summary, as needed):***
Nandini Bhattacharya, Ph.D. 03/17/2020

Xia Xu

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Nandini Bhattacharya

Digitally signed by Nandini Bhattacharya
Date: 3/18/2020 09:03:29AM
GUID: 508da70c00028f454473851fced0e9d4

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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ANIKA A LALMANSINGH
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