

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208845Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 208845

Review # 1

Drug Name/Dosage Form	Zilretta™(Triamcinolone Acetonide)Extended-Release Injectable Suspension
Strength	40 mg
Route of Administration	Intra-articular
Rx/OTC Dispensed	Rx
Applicant	Flexion Therapeutics, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
See List on first page of Drug Product Chapter		

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	OPQ/ONDP/DNDPAPI/BII
Drug Product	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV
Process	Pei-I Chu	OPQ/OPF/DPAII/BVI
Microbiology	Maria Martin Manso	OPQ/OPF/DMA/BI
Facility	Ebern Dobbin/Christina Capacci-Daniel Nazia Rahman	OPQ/OPF/DIA/BII CDRH/OC
Biopharmaceutics	Sandra Suarez/Haritha Mandula	OPQ/ONDP/DB/BII
Regulatory Business Process Manager	Steven Kinsley	OPQ/OPRO/RBPMI/BI
Application Technical Lead	Julia Pinto	OPQ/ONDP/DNDPII/BIV
Laboratory (OTR)	N/A	
ORA Lead	Caryn McNab/Michael Tollon	
Environmental Analysis (EA)	Valerie Amspacher	OPQ/ONDP/DNDPII/BIV

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Triamcinolone acetonide	1	17 Jun 2017	Reviewed by Sam Bain
	IV		(b) (4)	1, 4	22 Aug 2017	Reviewed validation of (b) (4) testing
	V			4, 7		Also see review by Maria Martin Manso for micro
	III			4		Vials for drug product
	III			4		Vials for drug product
	III			4		Vials for drug product
	III			4		Currently in use in approved products
	V			7		See review by Maria Martin Manso for micro
	V			7		See review by Maria Martin Manso for micro

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
CDRH OC	Complete	adequate	9/27/17	Nazia Rahman

Executive Summary

I. Recommendations and Conclusion on Approvability

Adequate data is provided to ensure the identity, quality and purity of the drug substance and drug product manufactured as described in this NDA. Further the overall facilities recommendation is adequate. Therefore this NDA is recommended for approval by the OPQ review team.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	Intra-articular injection for the management of osteoarthritis pain
Duration of Treatment	(b) (4)
Maximum Daily Dose	
Alternative Methods of Administration	None

B. Quality Assessment Overview

Zilretta® (triamcinolone acetonide) or FX006 is a sterile powder for suspension for intra-articular (IA) injection provided in a (b) (4) 5-mL glass vial containing (b) (4) mg of powder. The vial is filled with a copackaged diluent to deliver a 32-mg dose of triamcinolone acetonide (TCA). The drug product is prepared as an extended-release formulation of TCA formulated in 75:25 (b) (4) poly(lactic-co-glycolic acid) (PLGA) microspheres with a nominal drug load of 25% (w/w). The only excipient is the biodegradable PLGA polymer. (b) (4)

The vial is copackaged with a dilute vial. Prior to intra-articular IA administration, the drug product is reconstituted with 5 mL of sterile diluent containing 0.9% sodium chloride solution (normal saline), carboxymethylcellulose sodium (0.5% w/w), and polysorbate-80 (0.1% w/w), and mixed to form a suspension. (b) (4)

The drug product is supplied as a kit containing one FX006 drug product vial, one companion diluent vial, one vial adapter and prescribing information, contained in a secondary packaging carton. The proposed expiry of the FX006 diluent is (b) (4) months at a storage temperature of (b) (4) °C but it will be packaged with the drug product vial which has an expiry of 24 months. The two vials shoule

remain together within the same kit. Therefore the expiry for the entire drug product kit is 24 months when stored at (b) (4)

The manufacture, release and stability of the drug substance, triamcinolone acetonide, is referenced to DMF (b) (4). The DMF is adequate in support of the use of TCA in the preparation of the Zilretta® drug product. The retest date of (b) (4) is assigned to triamcinolone acetonide drug substance, (b) (4)

The process review of the drug product manufacture recommends the manufacture of Zilretta® as adequate. Sufficient data is provided to ensure the adequacy of the drug product from the biopharmaceutics prospective.

Drug substance and drug product facilities have been inspected with a recommendation of adequate. CDRH/OC has reviewed the vial adapter manufacturing for compliance of the 820 regulations. The CDRH/OC reviewer recommends the manufacturer as adequate in support of this NDA but with a post-marketing inspection required.

This NDA is recommended for approval.

Application Technical Lead Signature:

Julia C. Pinto, Ph.D.
Branch Chief(Acting)
ONDP/Division II/Branch IV



Julia
Pinto

Digitally signed by Julia Pinto
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BIOPHARMACEUTICS

Product Background:

NDA: 208845 ORIG-1

Drug Product Name / Strength: Zilretta™, 40 mg

Route of Administration: Intra-articular

Applicant Name: Flexion Therapeutics, Inc.

The Applicant is seeking approval of Zilretta™ (triamcinolone acetonide USP, extended release injectable suspension) as an intra-articular (IA) injection for the management of osteoarthritis pain. Zilretta™ (also referred as FX006) is an extended-release formulation of triamcinolone acetonide (TA) powder for injection. Zilretta™ formulation consists of TCA in 75:25 poly(lactic-co-glycolic) acid (PLGA) microspheres with a nominal drug load of 25% (w/w). Prior to administration, Zilretta™ is suspended in 5 mL of a companion diluent containing 0.9% sodium chloride, 0.5% carboxymethylcellulose sodium, and 0.1% polysorbate 80 (b) (4) (b) (4)

Zilretta™ is formulated to deliver TA to the synovial tissues for a period of approximately 3 months.

The development program follows the 505(b)(2) path relying, in part, on FDA's previous findings of safety and effectiveness for the reference listed drug (LD), Kenalog®-40 (TA, injectable suspension, USP). Comparative BA studies against the LD along with clinical data were also submitted in support of this NDA. Batches used in pivotal clinical trials were manufactured (b) (4) (b) (4) The Applicant intends to use (b) (4) for commercial and future clinical manufacturing of Zilretta™.

Review Summary:

This 505b (b)(2) drug product (microspheres) containing the drug substance TA is to be administered via intra-articular (IA) for the treatment of osteoarthritis pain. TA has been classified as BCS Class II drug substance. BCS classification is leveraged in support of biowaiver for orally administered drug products. Therefore, BCS class for this drug product is not relevant since it is to be administered IA. Zilretta™ is to be marketed as an ER drug product. Direct (local drug concentrations) and indirect (systemic exposure and degree of fluctuation) comparison of the drug product under review vs. an approved IR drug product support the ER claim.

The drug product underwent several manufacturing changes (e.g. site change) through the phases of development, which are considered major for an ER drug product. As agreed

during the IND stage, in vitro release profile comparisons were used to establish the bridge. These data along with a risk assessment approach which considers the control strategy support the approval of the site change/ manufacturing (minor) changes.

The following in vitro release method and acceptance criteria were agreed upon (refer to submission dated Aug 9, 2017):

Apparatus	USP 2 dissolution apparatus, rotating paddle
Medium	0.3% SDS in 10 mM phosphate buffer, pH 7.2 + 0.02% sodium azide (preservative)
Volume	1000 mL
Agitation	75 rpm
Temperature	35 °C
Sample	40 mg TCA (corresponding to ~ 160 mg of FX006 drug product)
Acceptance criteria	4 hours: NMT $\frac{(b)(4)}{(4)}\%$ 24 hours: $\frac{(b)(4)}{(4)}\%$ 48 hours: $\frac{(b)(4)}{(4)}\%$ 120 hours: NLT $\frac{(b)(4)}{(4)}\%$

Given the importance of microsphere PSD and its potential to impact in vitro release and in vivo performance, the Applicant was requested during the review cycle to revise their proposed PSD ranges. The following acceptance criteria for the microspheres PSD has been agreed upon (refer to submission dated 08/09/17):

$$\begin{aligned}
 PSD - D_{10} & NLT \frac{(b)(4)}{(4)} \mu m \\
 PSD - D_{50} & \frac{(b)(4)}{(4)} \mu m \\
 PSD - D_{90} & NMT \frac{(b)(4)}{(4)} \mu m
 \end{aligned}$$

The proposed control strategy is acceptable from biopharmaceutics perspective to assure product quality and performance and hence is adequate for lifecycle management of the product for changes within process/formulation ranges tested. However, during the lifecycle, if the changes are proposed beyond the ranges tested, depending on the criticality of the changes and its effect on drug product CQA and hence on product quality and performance, it would indicate a need of in vivo BE testing (e.g., SUPAC Level 3 process change).

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
--------------------	--------------

12/08/17	0000
3/16/2107	0007
06/13/17	0016
08/09/17	0024

Highlight Key Outstanding Issues from Last Cycle: NONE

Concise Description Outstanding Issues Remaining: NONE

From Biopharmaceutics perspective, NDA 208845 for Zilretta™. (Triamcinolone Acetone) ER Injectable Suspension, 40 mg is recommended for Approval.

BCS Designation

Reviewer's Assessment:

TA is practically insoluble in water. It belongs to a class II according to the Biopharmaceutics Classification System (BCS) with poor aqueous solubility (0.001 mg/mL) and high permeability (log P = 3.2)¹. The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. This information is leveraged in support of biowaiver for orally administered drug products. Therefore, BCS class for this drug product is not relevant since it is to be administered IA.

Polymorphism:

[Redacted content with (b) (4) markers]

IVR Method and Acceptance Criteria

IVR Method

As of August 2015, the USP Apparatus 2 based IVR method (Table 1) replaced Flexion's [Redacted] (b) (4). According to the Applicant, [Redacted] (b) (4).

[Redacted content with (b) (4) marker]

(b) (4)

Table 1 compares the (b) (4) and the current methods.

Table 1. Comparison of the IVR methods implement throughout drug product development

Parameter	(b) (4)	Current IVR Method
Period of use	All clinical development and stability studies through July 2015, including release of pivotal clinical batches and portions of the primary stability studies	Effective August 2015 replaces the (b) (4) method in ongoing stability studies and any subsequent batch release and stability studies
Apparatus	(b) (4)	USP 2 dissolution apparatus, rotating paddle
Medium		0.3% SDS in 10 mM phosphate buffer, pH 7.2 + 0.02% sodium azide (preservative)
Volume		1000 mL
Agitation		75 rpm
Temperature		35 °C
Sample		40 mg TCA (corresponding to ~ 160 mg of FX006 drug)
Sampling		4 hours, 24 hours, and 120 hours (5 days) Note that additional information-only time points may be collected for continued product assessment
Sample Analysis		HPLC, reverse phase with UV detection

The current IVR method development report was initially submitted to the IND dated July 1, 2015. This development report along with the full method validation report subsequently underwent a full review by FDA which resulted in written agreement that the IVR method is acceptable (February 9, 2016). According to the Applicant, the dominant release mechanism under the current release conditions (10 mM PBS, 0.3 % (w/v) SDS, 35°C) (b) (4)

IVR Discriminating Ability

The discriminating ability of the method was evaluated against the following attributes using batches manufactured at smaller R&D scale:

1. drug load,
2. polymer molecular weight, and
3. particle size/surface area of the microsphere.

The results of these studies are presented in Figures 1-3 which compared bot the (b) (4) and the current IVR method.

(b) (4)(b) (4)



Figure 3. Discriminating ability- Microsphere Particle Size Distribution

As noted above the discriminating ability of the method was evaluated using developmental batches. It is also noted that the set of DOE batches have a slower dissolution profile compared to the clinical and stability batches, similar to the observed particle size offset. On a response dated 6/14/17 following the FDA’s request, it was confirmed by the Applicant that the shift in performance is likely due to the scale of the experiments, which was approximately 1/10th the scale of the clinical and stability batches. According to the Applicant, in order to make a meaningful evaluation of the effect of the study parameters (e.g., polymer viscosity, suspension flow rate, PSD, etc.) with respect to the IVR specifications, the IVR data were re-scaled to account for the shift in performance between the clinical and stability batches and the DOE data set. For this purpose, the rate factor for each dissolution curve was determined by fitting the Weibull equation. A linear transposition of the rate factors was performed by equating the average rate factor of the small scale DOE midpoint batches with the average of the full scale clinical batches. According to the Applicant, re-scaling did not affect whether a parameter had a significant effect on IVR, and only affected the absolute value of the model constants. A visual representation behind calculations is shown in Figure 4.

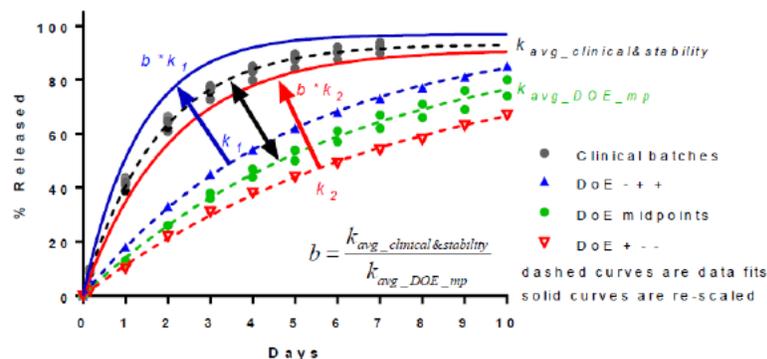


Figure 4. Visual representation of the re-scaling procedure

Based on this re-analysis, the following plots on the relationship between IVR and the critical attributes were obtained for the polymer MW based on DOE studies (Figure 5) and based on re-scaling (Figure 6) and for polymer ratio (showing re-scaling only, Figure 7).

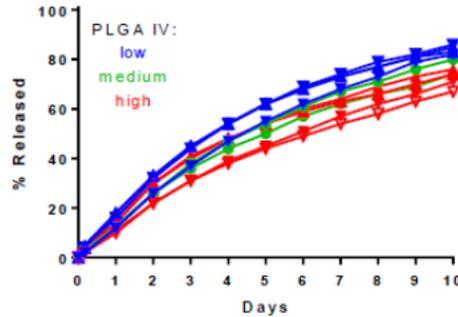


Figure 5. IVR curves of DOE batches for polymer weight effect.

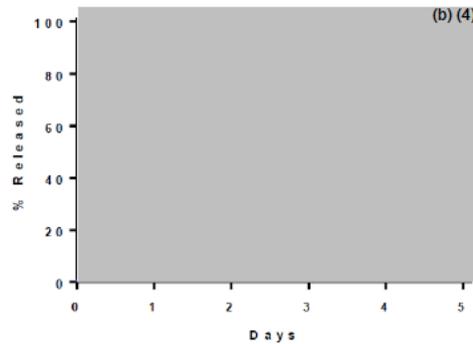


Figure 6. Re-scaling IVR Curves of DOE Batches with Specification Limits.

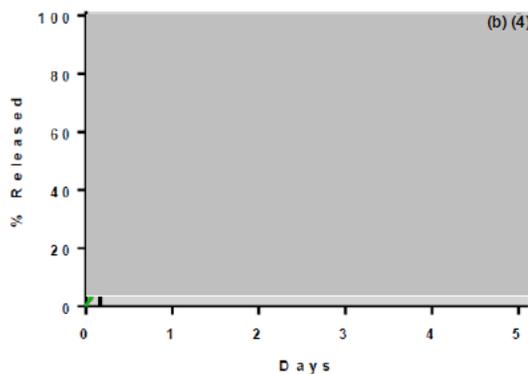


Figure 7. Rescaled IVR Curves for Batches Made with Copolymer Ratios of (b) (4) (Red), (b) (4) (Blue), and Target 75:25 (Green)

Reviewer's Comments

The reviewer agrees with the Applicant's assertion that the re-scaling analysis does not change the interpretation of the results when it comes to discriminating ability of the method. To this end, the acceptance criteria for *in vitro* release were revised to ensure the quality of the product throughout its life cycle.

However, the modeling approach assumes that the same level of interaction among the variables tested will occur upon scaling which may not hold true. Therefore, the CMC reviewer was advised during an OND meeting that ranges in the critical material attributes and process parameters should be set based on the characteristics of batches tested in pivotal Phase 3 Trials.

IVR Acceptance Criteria

The following acceptance criteria were originally proposed for the drug product under review. The data supporting these criteria are shown in Figure 8.

IVR Time Point	Acceptance Criteria
4 hours	NMT (b) (4) %
24 hours	(b) (4) %
120 hours	NLT (b) (4) %

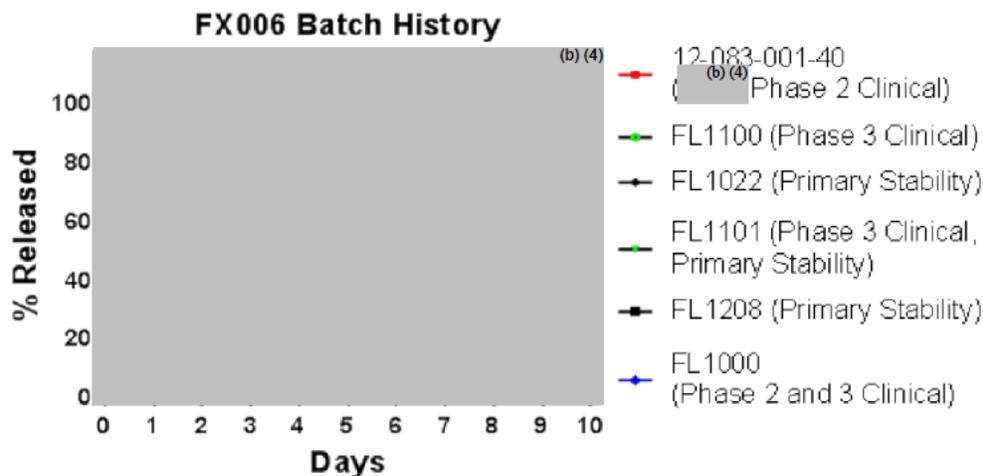


Figure 8. Typical IVR profiles for clinical pivotal batches.

Reviewer's comments

The ranges in acceptance criteria originally proposed may not be adequate to ensure consistent in vitro/in vivo performance throughout the life cycle of the drug product. Specifically, based on the results displayed on Figure 6, the proposed criteria may not be able to reject for aberrant batches (e.g. batches with larger polymer weight) as higher variation on the profiles are seen within 2 to 6 hours of the release testing. Therefore, during the review cycle (teleconference dated Aug 3, 2017) the Applicant was recommended to implement an additional time point after 48 hrs. of initiation of the test. On a response submitted Aug 9, 2017, the Applicant submitted an updated sheet of drug product specifications which reflect the Agency's recommendation as follows:

4 hours	NMT (b) (4) %
24 hours	(b) (4) %
48 hours	(b) (4) %
120 hours	NLT (b) (4) %

Reviewer's Assessment: ADEQUATE

The data provided demonstrated that the IVR method along with the recommended acceptance criteria are discriminating against critical quality attributes such as microsphere PSD, polymer weight and polymer ratio and will ensure consistent in vitro and in vivo performance of the drug product throughout its life cycle.

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment: NA

There are no data relating variations on the critical quality attributes, in vitro release and in vivo performance (e.g. systemic exposure) to evaluate the clinical relevance of the in vitro release specifications (method and criteria). Based on the in vitro data provided, the method will be able to reject for batches with inadequate performance on the critical attributes. In addition, the Applicant was recommended to (b) (4) the ranges for the microspheres PSD (see section below) to comply with those observed for the clinical batches.

Application of dissolution/IVIVC in QbD

According to the Applicant, the development performed for both at small scale and large scale, across different sites, justifies the commercial process to manufacture FX006 drug

product. The critical process for drug product performance, as measured by the critical quality attributes, particle size and in vitro release, (b) (4). Extensive studies were performed to map the performance of this process. According to the Applicant, the critical process parameters (CPPs) for the (b) (4) (b) (4) Studies were performed to understand the impact of these CPPs on product quality and to set appropriate operating ranges.

In a multivariate study, it was shown that (b) (4) affect the drug product particle size and therefore also IVR (Figure 9). The model effects of the parameters indicated that the ranges that were studied for both parameters will produce drug product within specification and are therefore considered PAR (Table 2). The Applicant claims that this was confirmed at full scale at (b) (4), where a change in the (b) (4) (b) (4) resulted in the expected change in particle size and hence IVR. Even though the data support (b) (4) for these two critical process parameters, they have a (b) (4) (b) (4) during a batch. This knowledge was applied to ensure that product quality was maintained upon scale-up to the commercial scale, (b) (4) (b) (4) For any injectable product, sterility is a critical quality attribute. For this drug product, sterility is ensured using (b) (4) (b) (4)

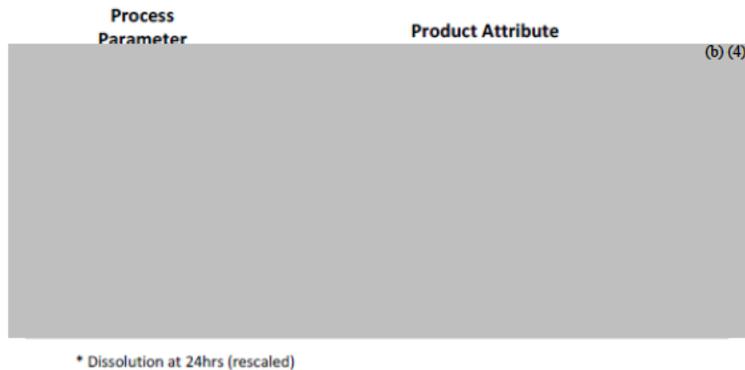


Figure 9. Schematic Correlating Process Parameters with Product Attributes

Table 2. Summary of (b) (4) Process Parameters



Given the importance of microsphere PSD and its potential impact on in vitro release, the Applicant was requested during the review cycle to provide the following data:

Provide data demonstrating that IVR testing is able to discriminate batches with PSD outside the ranges tested in pivotal phase 3 clinical trials. Alternative, set PSD ranges based on the characteristics of batches tested in pivotal phase 3 clinical trials.

On a submission dated 6/13/17, data were submitted showing that batches (b) (4) based on the proposed acceptance criteria (Table 7, Figure 14).

Table 7. Summary of FX006 Discrimination Batches

Batch Variable	Drug Load (% w/w)	PLGA MW	FX006 Particle Size (µm)		
			dV ₁₀	dV ₅₀	dV ₉₀
	Spec: (b) (4), (6)	Report Result	NLT (b) (4)	(b) (4)	NMT (b) (4)
Nominal	25	(b) (4) kDa	(b) (4)		
High Drug Load		(b) (4) kDa			
Low Drug Load		kDa			
Small PSD		kDa			
Low Polymer MW		kDa			

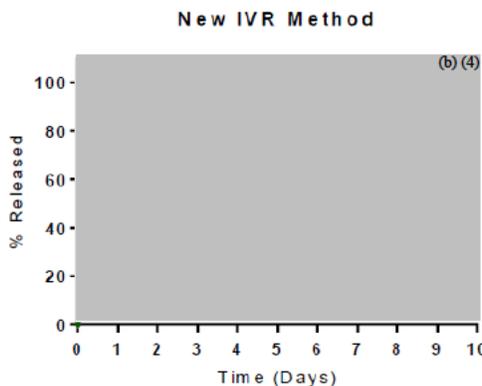


Figure 14. Discrimination Capability – FX006 Particle Size Distribution

Therefore, the following IR comment was conveyed to the Applicant:

- 1. We acknowledge the responses received on Jun 14, 2017 in terms of the particle size distribution (PSD) and its relationship with in vitro release data. The data provided up to date are not sufficient to support your proposed limits for PSD. Therefore, we recommend that you implement the following limits which are***

based on the performance of the pivotal clinical batches with some allowed variability:

PSD - D₁₀ NLT ^{(b) (4)} μm

PSD - D₅₀ ^{(b) (4)} μm

PSD - D₉₀ NMT ^{(b) (4)} μm

Submit updated table of specifications reflecting these recommended changes.

On a tecon dated 08/03/17, the Applicant agreed on ^{(b) (4)} the D10 and D50 as recommended above but proposed to set the D90 as NMT ^{(b) (4)} microns based on the following data:

1. Graphical comparisons of PSD and IVR trends for Pivotal Clinical, Primary Stability and Comparability batches: The results demonstrate that changes in particle size distribution do not correlate to changes in IVR within a given batch .
2. Graphical comparison of batches with the highest and lowest IVR curves and D90 PSD values among the Pivotal Clinical, Primary Stability, and Comparability Batches.
 - Employing a model independent approach to assess the equivalence of dissolution profiles, the similarity factor (f2) between the dissolution profiles for ^{(b) (4)} lot 066661, the fastest releasing comparability lot, and ^{(b) (4)} lot FL1000, the slowest releasing clinical lot, were calculated. An f2 factor of 60.0 was achieved, well above the minimum threshold of 50 that ensures equivalence of two profiles.
 - This comparison also demonstrates that D90 does not correlate to IVR across batches, since the slowest releasing batch is among the higher PSD-D90 samples, while the highest PSD-D90 batch releases intermediate to the other batches.
3. A summary of the range of D90 values observed on release and stability for each batch: The range of PSDs between the slowest IVR batch (FL1000) and the fastest IVR batch (066661) is broad, encompassing D90 values as low as ^{(b) (4)} μm and as high as ^{(b) (4)} μm, with no significant impact on IVR (Table 8).

Table 8. PSD Range of FX006 Batches on Release and Stability

Batch	Use	D10 Range (μm)	D50 Range (μm)	D90 Range (μm)
FL1000	Pivotal Clinical	^{(b) (4)}		
FL1100	Pivotal Clinical			
FL1101	Pivotal Clinical, Primary Stability			
FL1022	Primary Stability			
FL1022-inverted	Primary Stability			

FL1208	Primary Stability	(b) (4)
FL1223	Primary Stability	
066660	Comparability	
066661	Comparability	
066662	Comparability	

Reviewer’s Assessment: ADEQUATE

From Biopharmaceutics perspective, the proposed control strategy (including the in process controls attributes/parameters) are acceptable to assure product quality and performance; however, the ranges proposed (other than the PSD which was already revised upon the FDA’s request) may need to be revised given the revision of the acceptance criteria for dissolution and the effect due to scaling up.

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer’s Assessment: NA

This drug product is to be administered parenterally, and therefore, in vitro alcohol dose-dumping assessment is not applicable.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

During the review cycle, the Applicant was requested to provide evidence of extended release characteristics of their proposed product based on the following:

1. A bioavailability (BA) profile established for the drug product that rules out the occurrence of any dose dumping.
2. Data supporting that the drug product’s steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that was approved as an NDA.
3. Data supporting that the drug product’s formulation provides consistent pharmacokinetic performance between individual dosage units.
4. Data supporting that the drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.

On a submission dated 03/17/17, the Applicant provided sufficient information (summarized) as follows to support that their proposed product has ER characteristics:

1. Direct evidence:

According to the Applicant, direct evidence of ER properties comes from Clinical Pharmacology Studies 009, 005 and 002 through measuring the presence of TA in synovial fluid from the knee joint, which is the site of administration and site of action, for Zilretta. The results of Study 009 from synovial fluid showed prolonged presence of TCA post injection of Zilretta 40 mg (5 mL injection volume) compared with the same dose of a currently marketed uncontrolled form of TCA, Kenalog®-40 (immediate release TA). As shown in Table 3, at Week 6, which was the comparable sampling timepoint, the geometric mean (GM) was 3590.0 pg/mL for Zilretta 40 mg and 7.7 pg/mL for Kenalog-40, which was below the lower level of quantitation of the assay of 50 pg/mL TA. The drug substance was still present in Week 12 synovial samples from those patients who received Zilretta 40mg with a GM of 290.6 pg/mL demonstrating the ER properties of the drug product under review.

Table 3. Synovial Fluid Drug Concentrations (pg/mL) by Time Point FX006 Pooled across Cohorts (Synovial Fluid Drug Concentration Population)

Treatment Time	Number Below LLOQ	N	Mean	SD	Geometric Mean	Log-Scale SD	95 % CI	Median	Min, Max
FX006 40 mg									
Baseline (pre-treatment)	16	17	0.0	0.00	1.0	NA	1.00, 1.00	0.0	0, 0
Week 1	0	8	391063.4	221546.30	231328.9	1.69	56460.40, 947798.36	469104.8	4087, 670393
Week 6	1	6	45944.6	57251.92	3590.0	2.21	32.89, 391914.74	22928.0	0, 139494
Week 12	2	9	8258.6	19230.28	290.6	2.34	15.67, 5390.53	499.1	0, 58928
Week 16	2	2	0.0	0.00	1.0	NA	1.00, 1.00	0.0	0, 0
Week 20	4	4	0.0	0.00	1.0	NA	1.00, 1.00	0.0	0, 0
TCA IR (Kenalog-40)									
Baseline (pre-treatment)	3	5	0.0	0.00	1.0	NA	1.00, 1.00	0.0	0, 0
Week 6	6	8	1704.9	4439.15	7.7	1.81	0.31, 191.34	0.0	0, 12658

2. Indirect Evidence

Indirect evidence to support the ER claim is based on PK data generated through intensive plasma sampling collected in Studies -009, -002 and -001. The results of Study 009 showed that, the systemic concentrations of TA after Zilretta administration remained at that plateau over the first 24 hours post-dose and thereafter TA was slowly eliminated from the systemic circulation, through Weeks 1, 6, 12, 16, and 20 (see Figure 10). Comparatively, following the administration of the IR formulation, systemic concentrations remained within approximately 50% of the Cmax level over the first 24 hours post-dose and thereafter TA levels were decreased to a GM of 149.4 pg/mL by Week 6, (see Figure 10) supporting the ER characteristics of the drug product under review.

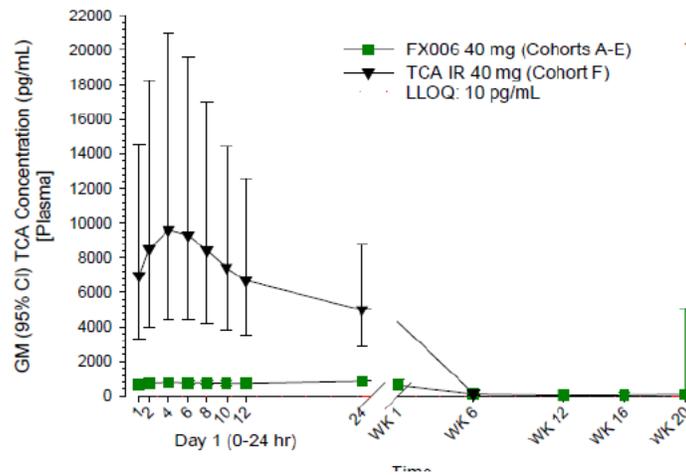


Figure 10. Geometric mean with 95% CI for Plasma Drug Concentrations (pg/mL) Curve - Zilretta and TCA IR (Plasma Drug Concentration Population).

In addition, data from Study FX006-2011-002 showed that the % fluctuation (Table 4) between peak (maximal value of the mean curve, observed on Day 1) and trough concentration values (i.e., minimal value of the mean curve, observed on Day 36-43) is markedly lower between peak and trough plasma concentrations of TCA as compared to TCA IR suggesting that IA administration of Zilretta resulted in a significantly slower release of TA from the site of injection into the plasma.

Table 4. Percent Fluctuation of TCA in Plasma following FX006 and TCA IR Administrations (Study FX006-2011-002)

TCA PK Parameters	Zilretta 40 mg	TA IR
Peak (pg/mL)	1008	29469
Trough (pg/mL)	157	47.8
C _{avg}	469	912
% Fluctuation	182	3226

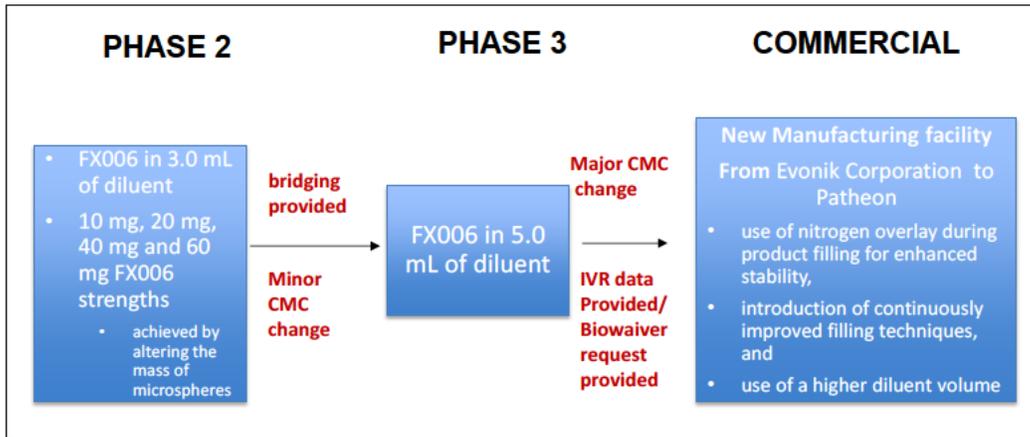
Note: C_{avg} = Calculated as $\frac{AUC_{0-1008}}{1008 \text{ h}}$
 % Fluctuation = Calculated as $100 \times \frac{(\text{Peak Concentration} - \text{Trough Concentration})}{C_{avg}}$

Reviewer’s Assessment: ADEQUATE

The in vivo PK data provided based on local and systemic concentration along with the characteristics of the PK and dosing regimen, support the extended release designation claim for Zilretta.

Bridging of Formulations

Figure 11 below summarizes the changes implemented during drug product development.



Phase 2 to Phase 3 Bridging

The process to manufacture Zilretta drug product was developed (b) (4)

The

changes implemented from phase 2 to phase 3 can be summarized as follows:

1. Batch 12-083-001, which was resuspended using **3 mL** of diluent prior to injection, was used in the Phase 2 dose-ranging exploratory efficacy trial, FX006-2011-001.
2. Batch FL1000 was used in the Phase 2b efficacy study and was resuspended **in 5mL** of diluent prior to injection.
3. Batches FL1000 and FL1100 were used in the pivotal Phase 3 clinical trial, which also used a diluent resuspension volume of **5 mL** prior to injection.

During the review cycle, the Applicant was requested to submit data bridging the Phase 2 and Phase 3 formulations. These changes are considered minor so that dissolution/in vitro release profile comparisons are considered sufficient to establish the bridge. On a submission dated March 17, 2017, dissolution data were submitted showing that the implemented changes do not have impact on the in vitro release as evident from the f2 values >50 (Figure 12, Table 5).

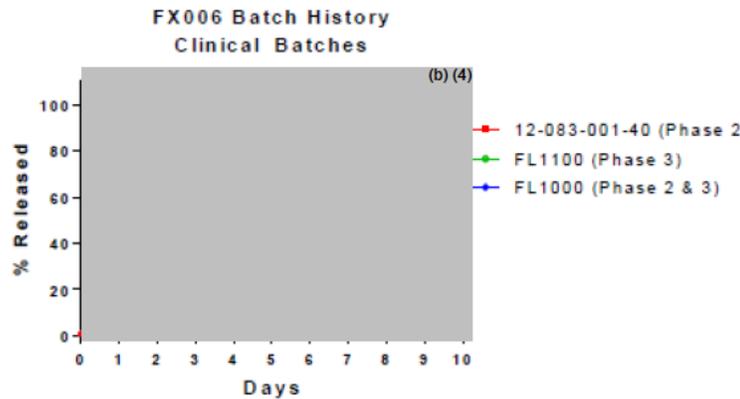


Figure 12. In vitro release profiles for batches tested in Phase 2 and Phase 3 trials.

Table 5. Statistical Comparison of IVR Profiles of Phase 2 vs Phase 3 Clinical Batches

Clinical Batches Comparison	Similarity Factor (F2)
FL1000 compared to 12-083-001	69
FL1000 compared to FL1100	70
FL1100 compared to 12-083-001	87

Phase 3 to Commercial Sites Bridging

The process to manufacture Zilretta drug product was developed (b) (4)

(b) (4)

Batches manufactured at (b) (4) were used for formal stability and pivotal clinical studies. For commercial manufacturing, the process was transferred (b) (4). These changes in manufacturing site are considered major for an extended release drug product such as Zilretta necessitating in vivo data (e.g. relative BA/BE) to establish the bridge. However, in a face-to-face Type C CMC Meeting on October 14, 2015, the Agency agreed that in vivo bioequivalence would not be necessary to support the proposed site change. Flexion proposed that a physico-chemical approach, such as the in vitro release (IVR) method, is the most accurate, sensitive, and reproducible approach to demonstrate bioequivalence based on the specific nature of Zilretta drug product and the analytical methods available. The Applicant added that due to the high inter-subject variability in PK, the physico-chemical approach is considered more reliable.

During the review cycle the Applicant was requested to submit a biowaiver request with supporting data. On a submission dated June 17, dissolution data were provided demonstrating that the in vitro release rate is not impacted by the change in manufacturing site (Figure 13, Table 6).

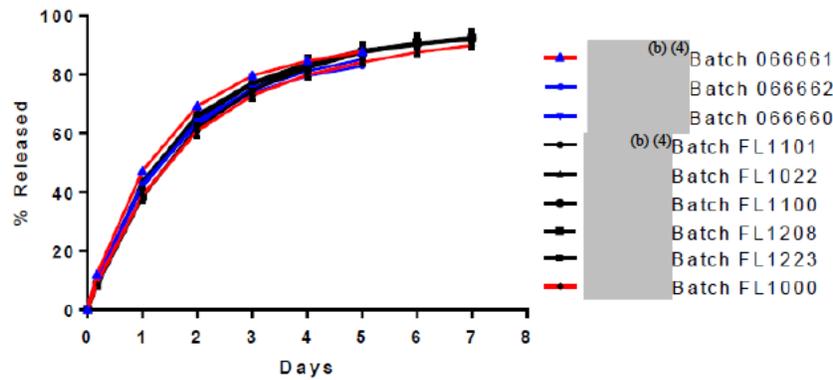


Figure 13. IVR Profile Comparison of (b) (4) Batches

Table 6. Similarity Testing (f_2 Values) Between Individual (b) (4) Batches

	(b) (4) Batches					(b) (4) Batches		
	FL1000	FL1022	FL1100	FL1101	FL1208	066660	066661	066662
FL1000		69.0	69.0	73.6	80.3	81.3	60.0	81.9
FL1022	69.0		97.4	93.1	76.4	81.6	79.4	73.2
FL1100	69.0	97.4		92.8	77.0	80.7	78.0	72.5
FL1101	73.6	93.1	92.8		83.2	87.5	73.4	76.3
FL1208	80.3	76.4	77.0	83.2		81.5	64.0	73.7
066660	81.3	81.6	80.7	87.5	81.5		68.7	88.5
066661	60.0	79.4	78.0	73.4	64.0	68.7		65.0
066662	81.9	73.2	72.5	76.3	73.7	88.5	65.0	

Reviewer’s Assessment: ADEQUATE

The data demonstrated that there is no change in in vitro release when changing manufacturing sites from (b) (4). It should be noted however, that as stated above, a change in manufacturing site is considered a major change for an ER formulation for which in vitro release/dissolution is not an appropriate endpoint. Nevertheless, based the pre-agreement during the IND state and on an email/discussion communication with the CMC reviewer Dr. Pei-I Chu on 2/24/17, she agreed with the Applicant that “We have taken measures to ensure that there have been no significant process, equipment, material, testing, or container closure changes” and added that “The applicant has conducted studies to demonstrate that the process parameters selected for the new/commercial facility will produce product that meet the proposed specifications”. Therefore, based on a risk-based approach which considered the understanding that the changes implemented only included the manufacturing site with other minor changes, the change in manufacturing site is considered acceptable from biopharmaceutics perspective.

Biowaiver Request

Reviewer’s Assessment:

See section above on bridging.

R Regional Information

Comparability Protocols**Reviewer's Assessment: NA*****Post-Approval Commitments*****Reviewer's Assessment: NA*****Lifecycle Management Considerations***

The proposed control strategy is acceptable from biopharmaceutics perspective to assure product quality and performance and hence is adequate for lifecycle management of the product for changes within process/formulation ranges tested. However, during the lifecycle, if the changes are proposed beyond the ranges tested, depending on the criticality of the changes and its effect on drug product CQA and hence on product quality and performance, it would indicate a need of in vitro BE testing (e.g., SUPAC Level 3 process change).

List of Deficiencies: NONE pending.**Comments conveyed to the Applicant as part of the 74-day letter:**

1. Submit the particle size distribution (PSD) values for batches used on the IVR method discriminating ability studies. These data are needed to support the proposed PSD specification for the microspheres.
2. Submit individual and mean IVT data for clinical batches FL1000, FL1100, and FL1101 and three additional representative GMP development batches (FL1022, FL1208, FL1223) used to set IVR acceptance criteria. Note that the acceptance criteria for IVT is set based on batches tested in pivotal clinical trials.
3. Provide a formal biowaiver request with supporting data/justification for the proposed manufacturing changes.
4. The following data should be submitted to support the extended release designation claim for your proposed drug product (refer also to CFR 320.25f):
 - a. The BA profile established for the drug product rules out the occurrence of any dose dumping;
 - b. The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
 - c. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;
 - d. The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.

5. Submit in vitro release profile comparison between the batches tested in phase 2 trials and phase 3 trials. These data are needed to establish the bridge between the formulations tested. Alternately, provide data demonstrating that the vehicle volume does not have an impact on the in vitro release of your proposed drug product.
6. Provide detail information of the scale up changes implemented from clinical to commercial sites with justification/data supporting the level of change.

Comments conveyed to the Applicant as part of the mid-cycle:

1. Submit the particle size distribution in terms of D10, D50 and D90 for all the pivotal phase 3 (manufactured (b) (4) and commercial batches (manufactured at (b) (4)
2. Provide data demonstrating that IVR testing is able to discriminate batches with PSD outside the ranges tested in pivotal phase 3 clinical trials. Alternative, set PSD ranges based on the characteristics of batches tested in pivotal phase 3 clinical trials.
3. Provide IVT profile comparisons with similarly testing between the batches manufactured (b) (4) These data should include the raw values.
4. The IVR data were re-scaled to account for the shift in performance between the clinical and stability batches and the DOE data set. For this, the rate factor for each dissolution curve was determined by fitting the Weibull equation. Provide detailed information/justification and assumptions made to demonstrate the validity of this approach.

Other Biopharmaceutics comments conveyed to the Applicant

We are in the process of reviewing your NDA and have identified some issues and the lack of some relevant information/data as follows. Before we can continue with the review of the biopharmaceutics related data and adequacy of the dissolution acceptance criteria, we request that you consider the following recommendation:

1. It is noted that the number of sampling times that are part of the dissolution acceptance criteria may not be sufficient to capture the variability of your drug product for quality control purposes. Therefore, implement an additional sampling point with the following acceptance criteria: (b) (4) %.
2. We acknowledge the responses received on Jun 14, 2017 in terms of the particle size distribution (PSD) and its relationship with in vitro release data. The data provided up to date are not sufficient to support your proposed limits for PSD. Therefore, we recommend that you implement the following limits which are based on the performance of the pivotal clinical batches with some allowed variability:

PSD - D₁₀ NLT (b) (4) μm
 PSD - D₅₀ (b) (4) μm

PSD - D₉₀ NMT (b) (4) μm

3. Please submit updated table of specifications reflecting these recommended changes.

Primary Biopharmaceutics Reviewer Name and Date:

Sandra Suarez Sharp, Ph.D. (Branch 2DB\ONDP\OPQ), August 18, 2017

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Mandula Haritha, Ph.D., Acting Team Lead (Branch 2\DB\ONDP\OPQ, August 22, 2017



Haritha
Mandula

Digitally signed by Haritha Mandula
Date: 8/23/2017 11:40:46AM
GUID: 508da6fb000282df41459408f32a1ce0

MICROBIOLOGY

Product Background

NDA: 208845

Drug Product Name

Proprietary: Zilretta™

Non-proprietary: Triamcinolone Acetonide

Strength: 32 mg

Route of Administration: Intra-articular

Applicant Name: Flexion Therapeutics, Inc.
10 Mall Road, Suite 301
Burlington, MA 01803

Manufacturing Site:

- **FX006 (powder for suspension) Manufacturing:** (b) (4)

- **FX006 diluent Manufacturing:** (b) (4)

Method of Sterilization:

(b) (4)

Review Recommendation: The submission is recommended for approval on the basis of sterility assurance.

Review Summary: The information provided by the applicant regarding container closure integrity testing, (b) (4) and, finished product specification and stability studies meets regulatory expectations and is sufficient to support the drug product manufacturing process from the standpoint of product quality microbiology. The proposed analytical procedures are adequate.

List Submissions Being Reviewed:

Submit	Received	Review Request	Assigned to Reviewer
08 December 2016	08 December 2016	N/A	19 December 2016
03 May 2017	03 May 2017*	N/A	N/A
14 June 2017	14 June 2017**	N/A	N/A
21 July 2017	21 July 2017***	N/A	N/A
15 August 2017	15 August 2017†	N/A	N/A
30 August 2017	30 August 2017††	N/A	N/A
11 September 2017	11 September 2017†††	N/A	N/A

*Quality / Microbiology Information; Quality / Response to Information Request

**Quality / Response to Information Request

***Multiple categories/Revised Labeling

†Quality / Response to Information Request

††Quality / Response to Information Request

††† Quality / Response to Information Request

Highlight Key Outstanding Issues from Last Cycle: Not applicable. This is a first cycle review.

Remarks: NDA-208845 was electronically submitted via gateway and provided in CTD format. All Module, Section, and pdf documents in this product quality microbiology review are from the submission dated 08 December 2016 unless otherwise noted.

Concise Description Outstanding Issues Remaining: Based on the information submitted in the application, no microbiology deficiencies were identified.

Supporting Documents:

The vial adapter was cleared by the FDA under the premarket notification provision of section 510(k) ^{(b) (4)}, as a class II medical device with the trade name ^{(b) (4)} Letter of Authorization (LOA) dated 12 June 2017 was provided. General Hospital Devices Branch (Inter-center Consult Memorandum) dated 9 June 2017 (approval recommended).

DME (b) (4)	Type	Holder	Subject (b) (4)	Microbiology Review
	V			D11648M33R01.doc Date 02/03/2017 Adequate
	V			D24888m04r01.docx Date 04/26/2017 Adequate*
	V			D20880MR11R01.doc Date 08/11/2016 Adequate

*See Reviewer's Comment in P.3.3

(b) (4)

List Number of Comparability Protocols (ANDA only): Not applicable

S DRUG SUBSTANCE

The drug substance (*i.e.* Triamcinolone acetonide, USP / Ph. Eur.)

(b) (4)

(b) (4) the drug substance specification includes the following acceptance criteria (module 2.3.S, drugsubstance3.pdf pages 3-4/11):

- Microbial count: TAMC (b) (4) CFU/g) and TYMC (b) (4) CFU/g). Absent of *E. coli*, *Salmonella sp.*, *S. aureus*, and *P. aeruginosa*.
- Bacterial endotoxins (NMT (b) (4) EU/mg).

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product –

Zilretta™ is supplied as a (b) (4) kit containing: vial-1 with 40 mg of sterile triamcinolone acetonide (TCA) extended release microsphere powder (*i.e.* FX006), vial-2 with 5 mL of sterile diluent, and a sterile vial adapter.

The vial adapter was cleared by the FDA under the premarket notification provision of section 510(k) (b) (4) The 510(K) holder is (b) (4)

The vial adapter is (b) (4)

The applicant has provided the following microbiological testing summary in response to an information request from the Center for Devices and Radiological Health (Module 1.11.1, appendix-14.pdf, dated 28 April 2017):

- Sterility dose confirmation (ISO 11137): (b) (4)
- Sterile barrier testing (*i.e.* visual inspection, peel test, bubble test, dye penetration test and seal strength).
- Bacterial endotoxins (USP <85>): (b) (4) EU/device.

Reviewer’s Assessment:

Acceptable

The information provided by the applicant regarding the vial adapter quality microbiology has been previously evaluated in the 510(k) referenced (b) (4). Therefore, this reviewer does not need to assess additional information.

• **Drug product composition –**

Vial-1 (FX006, powder for suspension):

Ingredient	Content per dose (mg)	Content per vial (mg)*
Triamcinolone acetonide, (b) (4) USP / Ph. Eur.	32	(b) (4)
75:25 Poly (D, L (b) (4) -co-glycolide) (b) (4) (PLGA) microspheres		(b) (4)

*The vial fill includes a (b) (4)% overfill to account for losses due to extractable volume limitations.

Vial-2 (FX006 diluent):

Ingredient	Content per dose of 5 mL (mg)
Sodium chloride, USP / NF / Ph. Eur.	(b) (4)
Carboxymethylcellulose sodium, USP / NF	
Polysorbate-80, USP / NF / Ph. Eur.	(b) (4)

• **Description of container closure system –**

Configuration	Component	Description	Manufacturer
FX006, powder for suspension*	Vial	5 mL, cerium (b) (4) USP type (b) (4) glass	(b) (4)

	Stopper	20 mm, (b) (4) gray (b) (4)	(b) (4)
	Seal	20 mm, aluminum crimp seal (b) (4)	
FX006 diluent	Vial	5 mL, type (b) (4) (b) (4) glass	
	Stopper	13 mm (b) (4) gray (b) (4)	
	Seal	13 mm, aluminum crimp seal (b) (4)	

* Updated on 14 June 2017 (module 3.2.P.7, container-closure-system1.pdf)

Reviewer's Assessment:

Acceptable

The information provided by the applicant regarding drug product composition and container closure system meets regulatory expectations.

P.2 Pharmaceutical Development



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OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

Application #: 208845	Established/Proper Name: Zilretta™
Applicant: Flexion Therapeutics, Inc.	Dosage Form: Extended-Release Injectable Suspension
Submission Type:	Strength(s): 40 mg
Chemical Type:	Cross Referenced Applications:

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	x		A list of comments included in the 74-day letter is attached at the end of this review.
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?			For Biopharmaceutics data needed, refer to appendix

A. OVERVIEW OF CRITICAL PRODUCT QUALITY REVIEW CONSIDERATIONS
<p><i>The drug product is a sterile powder for suspension, housed in a 5ml (b) (4) glass vial. The formulation is an extended-release composition comprising a 75:25 microspheres of PGLA: API (b) (4) triamcinolone acetonide (b) (4)). The (b) (4) powder vial is copackaged with a diluent and an adapter for transfer of the diluent into the powder vial. Once diluted the product is intended for intra-articular injection for the management of osteoarthritis (b) (4)</i></p>

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

B. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report (NME, API with estrogenic, androgenic, or thyroid activity; API derived from plants and animals) or appropriate categorical exclusion (21 CFR 25.31 AND 25.15(d) been provided?	x			
2.	For DMFs, are DMF #'s identified and authorization letter(s) from the US agent provided in the application and referenced DMF?	x			
3.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient information in the QOS to conduct a review?	x			
FACILITY INFORMATION					
4.	Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet with complete identifying information?	x			
5.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle?	x			
DRUG SUBSTANCE INFORMATION					
6.	Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in this section to conduct a review?	X			A DMF ^{(b) (4)} is referenced. Summaries of critical information are included in the NDA.
DRUG PRODUCT INFORMATION					
7.	Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in this section to conduct a review?	x			
BIOPHARMACEUTICS					
8.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?			x	The Clinical Pharmacology review team will be responsible for the review of all the relevant BA and BE studies included in this submission.
9.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or		x		The drug product underwent several manufacturing changes through the development program. From Phase 2 to

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NDA FILING REVIEW

B. FILING CONSIDERATIONS					
	manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>				Phase 3 clinical trials the drug product formulation underwent some formulation changes (e.g. volume of diluent was increased to 5 mL). These CMC changes are considered minor. Since the Applicant is relying on Phase 2 data to support the safety of the drug product, the Applicant will be requested to provide bridging data (e.g. in vitro release profile comparison). The commercial proposed site is different from the one used to manufacture the batches tested in pivotal Phase 3 trials. This change is considered major requiring BE data to support the bridge; however, the FDA agreed during the IND stage on the use of IVR data to support the change.
10.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.		x		No biowaiver was included. The Applicant will be requested to submit a formal biowaiver request in lieu of the required in vivo BE study to support the manufacturing site change.
11.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?			x	NA. Although this is a modified release formulation, the route of administration is via intraarticular.
12.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?		x		No. The applicant will be requested to submit this information as part of the 74-day letter
13.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?			x	NA
REGIONAL INFORMATION AND APPENDICES					
14.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		x		
15.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	x			
16.	If applicable, is the required information provided in 3.2.A for Biotech Products?			x	
17.	For Biotech Products, is sufficient information provided in compliance with 21 CFR 610.9 and 601.2(a)?			x	

OFFICE OF PHARMACEUTICAL QUALITY

NDA FILING REVIEW

APPENDIX

Summary of Biopharmaceutics Findings for Filing Purposes

Zilretta TM (FX006) is a novel extended release formulation of triamcinolone acetonide (TCA) in 75:25 poly(D,L-lactic-co-glycolic acid) (PLGA) microspheres developed by Flexion. This 505(b)(2) relies on the previous findings of safety and efficacy for Kenalog®-40 (TCA) approved under NDA 14,901 on Feb 1965. FX006 is an intra-articular (IA) injectable suspension for the management of osteoarthritis (OA) pain of (b)(4). The microsphere formulation is suspended in 5.0 mL of a companion diluent prior to administration. FX006 received Fast Track Designation in 2015.

According to the Applicant, clinical pharmacology studies demonstrated a favorable plasma PK profile of FX006 relative to immediate release TCA (TCA IR; Kenalog®-40), specifically with a much lower systemic exposure (lower C_{max} and AUC) compared to TCA IR. In addition, studies showed that the administration of FX006 resulted in prolonged retention of TCA in the synovial space of the knee with a controlled and stable release of TCA into the systemic circulation with low, plateauing concentration levels. The Applicant asserts that in the Phase 3 clinical study, the primary endpoint (reduction from baseline in average daily pain scores) as compared to placebo was met, which was further supported by favorable outcomes in a number of secondary endpoints.

A microsphere particle size range of (b)(4) µm was targeted for FX006 to allow the drug product to be administered intra-articularly through (b)(4) Ga needle (b)(4) micron and to achieve the desired TCA release rate. The Applicant claims that the dominant release mechanism under the current release conditions (10 mM PBS, 0.3 % (w/v) SDS, 35°C) (b)(4)

Throughout development, FX006 was suspended with the same companion diluent formulation. Early clinical studies suspended FX006 in 3.0 mL of diluent. Beginning with clinical study FX006-2014-006, the volume for suspension was increased to 5.0 mL to ensure adequate dose preparation and dispersion of product during injection. *Since data from this phase 2 study will be used to support the safety of the drug product, the applicant will be requested to provide appropriate data to support the bridging.* The primary changes that occurred during the course of clinical development are related to the site and scale of manufacture. GLP toxicology supplies and the first clinical batch of FX006 were manufactured (b)(4) with all remaining clinical and formal stability batches were manufactured (b)(4) . Commercial production will occur (b)(4) These CMC changes are considered major for an ER formulation requiring in vivo BE data to support its approval. However, during the IND stage, the FDA agreed on the use of IVR data to support the change based on the following data presented/claimed by the Applicant:

- The proposed IVR method is believed to be the most sensitive means of capturing changes in product performance.

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NDA FILING REVIEW

- The site change from [REDACTED] (b) (4) for this product does not represent a significant change with respect to product performance and that measures have been taken to ensure that there have been no significant process, equipment, material, testing, or container closure changes.
- Although the product is locally acting, some API is present in the plasma; however, the plasma concentrations being very low and highly variable. As a result, the PK data is highly variable.

The reviewer is of the opinion that the bridging is possible based on PK/PD endpoints without the need for establishing BE but BA (e.g. for safety purpose), which is more feasible from study design perspective (e.g. smaller sample size) in the case of highly variable drugs where a large sample size is needed to power the study. *Nevertheless, a risk based approach will be taken to address the bridging issue on the basis of:*

- *Data demonstrating the discriminating ability of the IVR method*
- *Applicant's assertion that "We have taken measures to ensure that there have been no significant process, equipment, material, testing, or container closure changes"*
 - *CMC input will be needed to ensure that no other changes (e.g. same process and equipment and in process controls are being utilized at the proposed manufacturing site) were implemented that indicate the need for additional data to support the bridge*

[REDACTED] (b) (4)

[REDACTED] Flexion established an IVR method that uses a USP Type 2 Apparatus operating at 75 rpm with a pH 7.2 aqueous buffered medium containing 0.3% SDS [REDACTED] (b) (4)

[REDACTED] Table 1 below summarizes the differences on these two methods. The FDA formally accepted current IVR method on February 9, 2016, based on data that included information supporting the discriminating ability and cross validation of the methods (e.g. [REDACTED] (b) (4) vs. current IVT method). The proposed acceptance criteria seem adequate on face value. The Applicant follow the guidance recommendation in terms of data points and ranges in the proposed criteria as follows:

IVR Time Point	Acceptance Criteria
4 hours	NMT [REDACTED] (b) (4) %
24 hours	[REDACTED] (b) (4) %
120 hours	NLT [REDACTED] (b) (4) %

OFFICE OF PHARMACEUTICAL QUALITY
NDA FILING REVIEW

Table 1. Proposed (current) in vitro release method for FX006

Parameter	(b) (4)	Current IVR Method
Period of use	All clinical development and stability studies through July 2015, including release of pivotal clinical batches and portions of the primary stability studies	Effective August 2015 replaces the (b) (4) method in ongoing stability studies and any subsequent batch release and stability studies
Apparatus	(b) (4)	USP 2 dissolution apparatus, rotating paddle
Medium	(b) (4)	0.3% SDS in 10 mM phosphate buffer, pH 7.2 + 0.02% sodium azide (preservative)
Volume	(b) (4)	1000 mL
Agitation	(b) (4)	75 rpm
Temperature	(b) (4)	35 °C
Sample	(b) (4)	40 mg TCA (corresponding to ~160 mg of FX006 drug product)
Sampling	(b) (4)	4 hours, 24 hours, and 120 hours (5 days) Note that additional information-only time points may be collected for continued product assessment
Sample Analysis	(b) (4)	HPLC, reverse phase with UV detection

Summary of Potential Biopharm Review Issues

1. No data were provided to support the ER designation claim.
2. The reviewer is of the opinion that the bridging of the commercial and clinical sites is feasible based on PK/PD endpoints without the need for establishing BE but BA (e.g. for safety purpose). Relative BA is more reasonable from study design perspective (e.g. smaller sample size) in the case of highly variable drugs where a large sample size is needed to power the study. Nevertheless, a risk based approach will be taken to address the bridging issue on the following basis:
 - a. Data demonstrating the discriminating ability of the IVR method
 - b. Applicant’s assertion that “We have taken measures to ensure that there have been no significant process, equipment, material, testing, or container closure changes”
 - i. CMC input will be needed to ensure that no other changes (e.g. same process and equipment and in process controls are being utilized at the proposed manufacturing site) were implemented that indicate the need for additional data to support the bridge

OFFICE OF PHARMACEUTICAL QUALITY
NDA FILING REVIEW

74-day letter comments (All Disciplines):

1. Your firm inadequately addressed the requirement for 21 CFR 820.20, Management Control. Please describe the organizational structure of your quality management system (i.e. organization chart) and explain how your firm controls all levels of the product development and manufacturing (i.e. supplier agreements).
2. Your firm inadequately addressed the requirement for 21 CFR 820.50, Purchasing Controls. Please summarize your procedure(s) for purchasing controls, including a description of the supplier evaluation process and the extent of control over suppliers. Also describe how it is ensured that products/services received are acceptable for their intended use and how changes made by subcontractors/suppliers will not affect the final combination product.
3. You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda>.
4. Provide a justification for the applicability of data collected in foreign study sites to the U.S. population or provide its location in the application. In particular, address differences in body mass index (BMI) between the U.S. population and the countries of the foreign study sites and how this may impact the interpretation of the study results.
5. Provide the data and propose release specifications for the following attributes of PLGA:

(b) (4)
6. Clarify whether the 24 hour in-use stability study included the use of the adapter to add the diluent. If so, provide any data for possible extractables that may have come from the adapter during transfer of the diluent to the powder vial.
7. Submit the particle size distribution (PSD) values for batches used on the IVR method discriminating ability studies. These data are needed to support the proposed PSD specification for the microspheres.
8. Submit individual and mean IVT data for clinical batches FL1000, FL1100, and FL1101 and three additional representative GMP development batches (FL1022, FL1208, FL1223) used to set IVR acceptance criteria. Note that the acceptance criteria for IVT is set based on batches tested in pivotal clinical trials.
9. Provide a formal biowaiver request with supporting data/justification for the proposed manufacturing changes.
10. The following data should be submitted to support the extended release designation claim for your proposed drug product (refer also to CFR 320.25f):

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- a. The BA profile established for the drug product rules out the occurrence of any dose dumping;
 - b. The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.
 - c. The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;
 - d. The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.
11. Submit in vitro release profile comparison between the batches tested in phase 2 trials and phase 3 trials. These data are needed to establish the bridge between the formulations tested. Alternately, provide data demonstrating that the vehicle volume does not have an impact on the in vitro release of your proposed drug product.
12. Provide detail information of the scale up changes implemented from clinical to commercial sites with justification/data supporting the level of change.



Sandra
Suarez

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Julia
Pinto

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