# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209310Orig1s000

# PRODUCT QUALITY REVIEW(S)

**Recommendation: Approval**

# NDA 209310
# Review #1

| | |
|---|---|
| Drug Name/Dosage Form | Mometasone furoate implant |
| Strength | 1350 mcg/implant |
| Route of Administration | Implanted into sinus |
| Rx/OTC Dispensed | Rx |
| Applicant | Intersect ENT, Inc. |
| US agent, if applicable | |

| SUBMISSION(S) REVIEWED | DOCUMENT DATE | DISCIPLINE(S) AFFECTED |
|---|---|---|
| *Original* | *07-MAR-2017* | *all* |
| *Amendment* | *31-MAY-2017* | *microbiology* |
| *Amendment* | *26-JUN-2017* | *biopharmaceutics* |
| *Amendment* | *05-SEP-2017* | *biopharmaceutics, process/facilities, microbiology* |
| *Amendment* | *18-SEP-2017* | *drug product* |
| *Amendment* | *19-SEP-2017* | *microbiology* |
| *Amendment* | *31-OCT-2017* | *biopharmaceutics* |
| *Amendment* | *13-NOV-2017* | *process/facilities* |
| *Amendment* | *16-NOV-2017* | *drug product (labeling)* |

**Quality Review Team**

| DISCIPLINE | REVIEWER | DIVISION/BRANCH |
|---|---|---|
| Drug Substance | Monica Cooper | ONDP/DNDAPI/NDBI |
| Drug Product | Monica Cooper | ONDP/DNDAPI/NDBI |
| Process | Joanne Wang | OPF/DPAII/PABIV |
| Microbiology | Jason God | OPF/DMA/MABII |
| Facility | Daniel DeCiero | OPF/DIA/IABII |
| Biopharmaceutics | Hangsong Chen | ONDP/DB/BBII |
| Regulatory Business Process Manager | Florence Aisida | OPRO/DRBPMI/RBPMBI |
| Application Technical Lead | Craig M. Bertha | ONDP/DNDPII/NDPBIV |

| | | |
|---|---|---|
| Laboratory (OTR) | N/A | |
| ORA Lead | Ashar Parikh<br>Lucila Nwatu | OMPT/OPQO/DPQOIV/PQIB |
| Environmental Analysis (EA) | See drug product chapter | |

# 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) | | Adequate | 15-AUG-2017 | IR sent regarding updating DMF to current USP for elemental impurities testing |
| | III | | | Not reviewed | | Sufficient information in NDA |
| | III | | | Not reviewed | | Sufficient information in NDA |
| | III | | | Adequate | 27-OCT-2017 | |

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

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| IND | 116042 | MF sinus implant for the treatment of sino-nasal symptoms associated with ethmoid sinus obstruction |
| | | |

## 2. CONSULTS

| DISCIPLINE | STATUS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|---|
| Biostatistics | N/A | | | |
| Pharmacology/ Toxicology | final | no safety concern re: (b) (4) (b) (4) impurity | 01-AUG-2017 | Dr. L. Pei |
| CDRH | N/A | | | |
| Clinical | N/A | | | |
| Other | | | | |

# Executive Summary

## I. Recommendations and Conclusion on Approvability

*N/A, application is recommended to be approved*

## II. Summary of Quality Assessments

### A. Product Overview

The sinus implant from Intersect ENT is a combination product (drug-device) that consists of a bioabsorbable sinus stent that is coated with mometasone furoate (MF). The implant is also to be marketed with a crimper and delivery system for implantation. The product is said to have sufficient mechanical strength to improve obstruction in the ethmoid sinus of patients. The release of the MF from the implant is intended for its anti-inflammatory properties and the combination product is to be used to treat (b) (4) polyps, in adults that have had ethmoid sinus surgery.

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | (b) (4) |
| **Duration of Treatment** | Implant can remain up to 90 days |
| **Maximum Daily Dose** | N/A |
| **Alternative Methods of Administration** | N/A |

### B. Quality Assessment Overview

SINUVA is a Mometasone furoate (corticosteroid)-eluting implant indicated for the treatment of (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery. This is a drug-device combination product.

The drug substance mometasone furoate (b) (4) is a white to off-white powder, which is soluble in acetone and dichloromethane, slightly soluble in ethanol, and practically insoluble in water. The drug substance is manufactured, tested, and packaged by (b) (4) Detailed information on the chemistry, manufacturing, and controls of the drug substance was referenced to (b) (4) DMF (b) (4) see separate review of DMF (b) (4) which was found to be

adequate).

The Sinuva S8 nasal implant, which is manufactured from synthetic bioabsorbable copolymers [poly(L-lactide-co-glycolide)], is coated with mometasone furoate (1350 mcg total drug content) that is embedded in a bioabsorbable polymer matrix containing (b) (4) poly(DL-lactide-co-glycolide) and polyethylene glycol (inactive ingredients), which provide for gradual release of the drug. (b) (4)

(b) (4)

. The registration stability data support the applicant's proposed expiration date of **24 months** for the finished product when stored in the commercial packaging (protected from light) at controlled room temperature.

The manufacturing process involves (b) (4) and has found it to be adequate.

The drug product has a quality test in place to assess drug release or dissolution, and the biopharmaceutics review focused on the dissolution method development report, discriminatory power, dissolution data, and specification. The applicant developed their in-house dissolution method for their proposed product as a quality control tool and it is considered acceptable. The following specifications were set as agreed upon with the Applicant:

1 hour: (b) (4)
3 hours: (b) (4)
24 hours: (b) (4)

From the facilities perspective, the application is also found to be acceptable. The majority of the sites were found to be acceptable based on their inspectional history, with the exception of the drug product manufacturer, Intersect ENT. Inc. A pre-approval inspection was conducted at Intersect and focused primarily on the drug coating process, since the firm had been previously inspected for similar implant products from a device perspective. A form 483 was issued and the firm's responses have been evaluated and have been found to be acceptable.

**C. Special Product Quality Labeling Recommendations (NDA only)**

The labeling for this combination product will vary to be consistent with the labeling for the previously approved mometasone furoate sinus implants already cleared by CDRH

**D. Final Risk Assessment (see Attachment)**

# DRUG SUBSTANCE

(b) (4)

[redacted]

(b) (4)

(b) (4)

## S.2 Manufacture

(b) (4)

(b) (4)

(b) (4)

[redacted]

(b) (4)

(b) (4)

## S.7 Stability

***Summary of Stability Data (S.7.1 and S.7.3)***

Detailed information on the stability of the drug substance was referenced to (b) (4) DMF (b) (4) The manufacturer has studied the stability of MF in both packa systems I and II.

**Reviewer's Assessment: ACCEPTABLE**. See DMF (b) (4) and Review #12 (M. Cooper) for more details.

***Post-Approval Stability Protocol and Commitment (S.7.2)***

Detailed information on the post-approval stability protocol and stability commitment for the drug substance was referenced to (b) (4) DMF (b) (4)

**Reviewer's Assessment: ACCEPTABLE**. See DMF (b) (4) and Review #12 (M. Cooper) for more details.

## R Regional Information

***Comparability Protocols***
None.

***Post-Approval Commitments***
None.

***Lifecycle Management Considerations***
None.

***List of Deficiencies:***
None.

***Review Recommendation:***

Based on material provided by the Applicant, **approval of** this NDA is recommended from the drug substance perspective.

***Primary Drug Substance Reviewer Name and Date:***

Monica D. Cooper, Ph.D.
Review Chemist
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
10-27-2017

***Secondary Reviewer Name and Date:***

Concurrence: I concur with the recommendation of the primary drug substance reviewer.

Benjamin D. Stevens, Ph. D., M.P.H.
Acting Branch Chief
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
10-27-2017

Monica Cooper

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Ben Stevens

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# DRUG PRODUCT

(b) (4)



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(b) (4)

[redacted]

## R Regional Information

***Environmental Assessment***

The applicant stated that this NDA for the S8 Sinus Implant, 1350 mcg mometasone furoate per implant, qualifies for categorical exclusion from performing an environmental assessment report per 21 CFR 25 and *Guidance for Industry – Environmental Assessment of Human Drug and Biologics Applications, Revision 1, July 1998*. The applicant stated that the categorical exclusion claim is based on the fact that the requested action, approval of NDA 209310, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(b). To the applicant's knowledge, no extraordinary circumstances exist that woul warrant the preparation of an EA.

***Reviewer Notes***: The applicant did not provide any calculations to show that the estimated concentration of the active moiety at the point of entry into the aquatic

environment is less than 1 ppb. The following information request was sent to the applicant on 24-Aug-2017:

- ***You requested a categorical exclusion from performing an environmental assessment report per 21 CFR 25.31(b). However, you did not provide any calculations of the expected introduction concentration (EIC) of the active moiety into the aquatic environment due to increased use. To determine the appropriateness of the exclusion request, provide the missing calculations.***

***Response***: In the **Amendment dated 18-Sep-2017**, the applicant revised the request for categorical exclusion from performing an environmental assessment to include the calculations recommended in the Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (see detailed calculation below). The amount calculated (b) (4) ) is smaller than the threshold of 1 ppb; therefore, an environmental assessment is not required.

(b) (4)

***Methods Verification Package***

Method validation information was provided for the non-compendial methods used for the drug product (see summaries of the applicant's method validation reports earlier in this review).

**Reviewer's Assessment**: **ACCEPTABLE**. This reviewer (MDC) had no concerns with the non-compendial methods for the drug product. No methods were sent to the Agency labs for independent verification.

***Comparability Protocols***
None.

***Post-Approval Commitments***
None.

***Lifecycle Management Considerations***
None.

***List of Deficiencies***
None.

***Review Recommendation:***

Based on material provided by the applicant, **approval of** this NDA is recommended from the drug product perspective.

***Primary Drug Substance Reviewer Name and Date:***

Monica D. Cooper, Ph.D.
Review Chemist
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
03-Nov-2017

***Secondary Reviewer Name and Date:***

Concurrence: I concur with the recommendation of the primary drug product reviewer.

Benjamin D. Stevens, Ph. D., M.P.H.
Acting Branch Chief
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
03-Nov-2017

Monica Cooper

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Ben Stevens

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# BIOPHARMACEUTICS

**Product Background:**

The Applicant, Intersect ENT, developed Mometasone Furoate Sinus Implant, 1350 mcg. This corticosteroid-eluting implant is a self-expanding and bioabsorbable combination drug-device product, which is designed to be placed in the ethmoid sinus cavity. The proposed indication is for the treatment (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery. The Applicant submitted this application to the Agency on 3/7/2017 and seeks an approval through 505(b)(2) pathway.

**NDA/ANDA:** NDA 209310

**Drug Product Name / Strength:** Mometasone Furoate Sinus Implant, 1350 mcg

**Route of Administration:** Sinus Implant

**Applicant Name:** Intersect ENT

***Review Summary:***

Biopharmaceutics review focuses on the dissolution method development report, discriminatory power, dissolution data, and specification.

The Applicant developed their in-house dissolution method for their proposed product as a quality control tool. The dissolution method was reviewed and considered acceptable. However, the initially proposed specifications were not set appropriately. The following specifications were set as agreed upon with the Applicant:
1 hour: (b) (4)
3 hours: (b) (4)
24 hours (b) (4)

From the Biopharmaceutics perspective, this Reviewer recommends that NDA 209310 Mometasone Furoate Sinus Implant, 1350 mcg is ADEQUATE for approval.

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

| | |
|---|---|
| 3/7/2017 | NDA 209310/Original submission |
| 6/26/2017 | eCTD-0006/Response to Biopharmaceutics Information Requests |
| 9/5/2017 | eCTD-0011/Response to Biopharmaceutics Information Requests |
| 10/23/2017 | eCTD-0017/Response to Biopharmaceutics Information Request |

**Highlight Key Outstanding Issues from Last Cycle:**

**Concise Description Outstanding Issues Remaining:**

*None.*

***BCS Designation***

**Reviewer's Assessment:** The Applicant did not report Mometasone Furoate's BCS classification.

**Solubility:** Not reported.

**Permeability:** Not reported.

**Dissolution:** See the Biopharmaceutics review.

***Dissolution Method and Acceptance Criteria***

**Reviewer's Assessment:**

**I. Information Request (IR) 1**

On 6/12/2017, the FDA sent a Biopharmaceutics IR to the Applicant. On 6/26/2017, the Applicant responded to the IR. The following are the IR, the Applicant's response and this Reviewer's assessment of the Applicant's response.

**IR 1 Item 1**

You stated that the proposed dissolution method was developed by utilizing the US dissolution developmental methodology along with the knowledge gained from the commercial Propel products as the starting point. However, the dissolution method development report for the Proposed Drug product - mometasone furoate, sinus implant 1350 mcg could not be located in the submission. Submit the report to the Agency for review.

**The Applicant's response to IR Item 1**

The Applicant stated that they submitted the dissolution method development report R-35049, which is included in updated 3.2. P.2.2.

**Reviewer's comment**

*The response is not adequate. The Applicant failed to provide the detailed information about how they selected the key parameters (apparatus, rotation speed, and dissolution medium) for their proposed dissolution method in the dissolution method development report.*

**IR 1 Item 2**

You stated that the proposed dissolution method has discriminating ability towards the composition change in the formulation, (b) (4)

**The Applicant's response to IR 1 Item 2**

(b) (4)

**Reviewer's comment**

*The response is not adequate.* (b) (4)

## II. Information Request (IR) 2

On 8/2/2017, the FDA sent the second Biopharmaceutics IR to the Applicant. On 9/5/2017, the Applicant responded to the IR. The following are the IR, the Applicant's response and this Reviewer's assessment of the Applicant's response.

**IR 2 Item 1**

In the previous Biopharmaceutics Information Request (IR), we requested you to submit a full dissolution method development report to the Agency for review. With the IR response, you submitted the updated Intersect ENT Report R-35049.
After reviewing this report, we concluded that you did not provide sufficient data as requested. For example:

(b) (4)

Resubmit a full dissolution method development report to the Agency for review.

**The Applicant's response to IR 2 Item 1**

The Applicant stated that they revised the dissolution method development report R-35049, Release Rate Method Development Report for S8 Sinus Implant to address FDA's request. Report R-35049 is attached in the response to this IR.

**Reviewer's comment**

*The response is adequate. The dissolution method development report R-35049 was thoroughly reviewed under Section V. Dissolution Method development.*

**IR 2 Item 2**

In the response to our IR Item 2, you stated tha (b) (4)

Submit the study report to the Agency for review.

**The Applicant's response to IR 2 Item 2**

The Applicant stated that they clarified the role of (b) (4)

**Reviewer's comment**

*The response is adequate. Study Report R 23006 Rev C was reviewed thoroughly under Section V. Dissolution Method development.*

**IR 2 Item 3**

Submit the complete dissolution data (individual, mean, SD, RSD, and profile) of the following batches to the Agency for review:

**RESOLVE II**

C41106001 (Table 1)
C50226004 (Table 2)

**RESOLVE**

C21130002 (Table 6)
C21207001 (Table 7)
C30304001 (Table 8)
C30401001 (Table 9)
C30604002 (Table 10)
C30530001 (Table 11)
C30918001 (Table 12)

**The Applicant's response to IR 2 Item 3**

The Applicant stated that they provided the requested data in Tables 1, 2 and Tables 6 through 12, which are included in the response to this IR.

**Reviewer's comment**

*The response is adequate. The data were reviewed under VI. Dissolution data and specifications.*

**IR 2 Item 4**

Clarify why you decided to (b) (4)

**The Applicant's response to IR 2 Item 4**

The Applicant observed variability in (b) (4)

Table 1. Release Rate Data Comparing %RSD for lots (b) (4)

(b) (4)

**Reviewer's comment**

*The response is adequate.*

**IR 2 Item 5**

In RESOLVE and RESOVE II studies, you used different lots manufactured with different manufacturing processes (tighter environmental control). Provide a scientific justification with sufficient supporting data whether the reduction in the variability of the in vitro release rate caused by the change in manufacturing process will have an impact on the vivo pharmacokinetics performance of the proposed product.

**The Applicant's response to IR 2 Item 5**

The Applicant stated that the PK study demonstrated that mometasone furoate blood plasma concentration levels are undetectable or negligible from the sino-naso route of administration. However, the Applicant stated that the reduction in the variability of the in vitro release rate caused by the change in manufacturing process will have no impact on the vivo pharmacokinetics performance of the proposed product, because the lots manufactured with the (b) (4) process have similar dissolution profiles.

The Applicant calculated the average release rate of all batches manufactured (b) (4)

Table 2. Similarity Factor Calculations—Resolve, Resolve II Manufacturing Process Release Rate Profile Comparison

(b) (4)

Figure 1. S8 In-Vitro Dissolution (Release Rate) Profile Comparison

S8 In Vitro Release Rate (Dissolution) Profile Comparison
(error bars represent standard deviation)

(b) (4)

Timepoint (hrs)

**Reviewer's comment**

*In the response, the Applicant used the pooled data to compare the similarity between the pre-change and post-change lots. The dissolution data in Appendixes show that the percent coefficient of variation of most pre-change batches are within acceptance range* (b) (4) *except Batches C30304001 and C30401001. However, the inter-batch variation is high, the comparison result based on the pooled data does not reflect the actual similarity between individual pre-change lots and individual post-change lots.*

*Under Section Bridging of Formulations, this Reviewer compared each pre-change clinical batch with one representative post-change batch (C50428002), and found that four out of seven batches manufactured* (b) (4) *are similar to C50428002 in dissolution profiles based on the calculated similarity factors.*

*Although a definite conclusion could not be drawn whether the batches manufactured with* (b) (4) *are similar to the batches manufactured with the* (b) (4) *method*

*in dissolution profiles, it is still acceptable because it is a minor manufacturing change. This assessment was confirmed by the Drug product and Process Reviewers.*

**IR 2 Item 6**

Because you used different lots manufactured with different manufacturing processes (tighter environmental control) in RESOLVE and RESOVE II studies, you need to use appropriate data (bioequivalent studies or dissolution profile comparison) to bridge the products manufactured with different processes.

**The Applicant's response to IR 2 Item 6**

The Applicant stated that the lots manufactured with the original (b) (4) process and the lots with the (b) (4) process (tighter environmental control) are similar in the dissolution profiles based on the results from IR Item 5.

**Reviewer's comment**

*Refer to this Reviewer's comments to IR 2 Item 5.*

## III. Drug product

(b) (4)

(b) (4)

[redacted]

(b) (4)

## IV. Dissolution Method

The Applicant proposed the following dissolution method:

Table 5. Dissolution method developed by the Applicant

| | Mometasone Furoate, sinus implant, 1350 mcg |
|---|---|
| Apparatus | USP apparatus –II (paddle) |
| Speed | 50 rpm |
| Dissolution media | 2.0% SDS in water |
| Volume | 500 mL |
| Time (min) | 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr. |
| Temperature | 37 ± 0.5 °C |
| Initially proposed specifications | 1 hour: (b) (4)%<br>3 hours: (b) (4)%<br>24 hours: NLT (b) (4)% |

(b) (4)

***List of Deficiencies:***

*None*

***Primary Biopharmaceutics Reviewer Name and Date:***

*Hansong Chen, PharmD, Ph.D., 10/15/2017, 10/23/2017, 11/3/2017*

*Biopharmaceutics Reviewer*

*OPQ/ONDP/DB*

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

*Haritha Mandula, Ph.D., 11/3/2017, 11/7/2017*

*Acting Biopharmaceutics Quality Assessment Lead*

*OPQ/ONDP/DB*

Hansong Chen

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Haritha Mandula

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# PROCESS

**Review Recommendation: Adequate from Process perspective.**

**NDA: 209310**

**Drug Product Name / Strength: Mometasone furoate sinus implant SINUVA™ / 1350 mcg per implant.**

**Route of Administration: Sino-nasal**

**Applicant Name: Intersect ENT, Inc.**

**Notes: 505(b)(2). Relied upon Asmanex Twisthaler, 110 mcg, 220 mcg; NDA 021067**

***Review Summary:***

SINUVA is a Mometasone furoate (corticosteroid)-eluting implant indicated for (b) (4) (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery. This is a drug-device combination product.

The manufacturing process involve (b) (4) Overall the process risk is medium, but it is adequately mitigated with the proposed control strategy.

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

| Document(s) Reviewed (SD-#) | Date Received |
|---|---|
| Original Submission | 3/7/2017 |
| Response to FDA August 2, 2017 Request for Information | 9/5/2017 |
| Response to FDA November 02, 2017 Request for Information - CMC | 11/13/2017 |

**Highlight Key Outstanding Issues from Last Cycle: N/A**

**Concise Description Outstanding Issues Remaining: N/A**

**P.3 Manufacture**

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(b) (4)

[redacted]

***Summary of Process Validation Studies Conducted N/A***

***Assessment of Microbiological Controls: Reviewed by Microbiology Reviewer***

***Comparability Protocols N/A***

***Post-Approval Commitments***

**Applicant Commitment Received on November 13, 2017:** Intersect ENT hereby acknowledges that (b) (4) [redacted].

***Primary Process Reviewer Name and Date: Chiaochun Joanne Wang, Ph.D. 11/14/2017***

***Secondary Reviewer Name and Date: Chengjiu Hu, Ph.D, 16Nov2017***

Joanne Wang

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Chengjiu Hu

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# MICROBIOLOGY

**Product Background:** The drug product i (b) (4)

**NDA:** 209310

**Drug Product Name / Strength:** Mometasone furoate sinus implant / 1350 µg

**Route of Administration:** Sino-nasal implant

**Applicant Name:** Intersect ENT, Inc.

**Manufacturing Site:**
Intersect ENT, Inc.
1555 Adams Dr.
Menlo Park, CA 94025

**Method of Sterilization:** (b) (4)

***Review Recommendation:*** Adequate

***Review Summary:*** The drug product is (b) (4)

**List Submissions Being Reviewed:**
03/07/2017
09/05/2017
09/18/2017

**Highlight Key Outstanding Issues from Last Cycle:** N/A

**Remarks:** Information requests were issued by the Agency, 2 August 2017 and 8 September 2017. The applicant's responses, received 5 September 2017 and 18 September 2017, have been incorporated into the appropriate sections of this review.

**Concise Description Outstanding Issues Remaining:** (None)

**Supporting Documents:** (None)

**List Number of Comparability Protocols (ANDA only):** N/A

## P.1 Description of the Composition of the Drug Product

(b) (4)

[redacted]



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(b) (4)

**Reviewer's Assessment: A*dequate.***
The drug product specification (sterility testing) and validation comply with USP <71> Sterility Test, as well as FDA Guidance for Industry: Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.

## P.8 Stability

### P. 8.1 Stability Summary and Conclusion

Stability studies are ongoing for samples stored under long-term (25°C±2°C/60%±5%RH) and accelerated (40°C±2°C/75%±5%RH) conditions.

### P. 8.2 Post-Approval Stability Protocol and Stability Commitment

Ongoing formal stability studies will be continued through the 24-month time point for samples stored under long-term conditions. Annually thereafter, at least one lot of approved drug product will be placed on long-term stability.

### P.8.3 Stability Data

Data provided through 12 months of testing shows no deviations for sterility or package integrity.

## R Regional Information

***Executed Batch Records***
The executed batch record for lot # Q50803001 is provided.

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

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

***2.A. Package Insert***
Drug product device is to be stored at 20-25°C.

***List of Deficiencies:*** (None)

***Primary Microbiology Reviewer Name and Date:*** Jason M. God, Ph.D., 09/25/2017

***Secondary Reviewer Name and Date:*** Denise A. Miller, 10/02/2017

Denise Miller

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Jason God

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# FACILITIES

**Product Background:** First Review

The drug product is a sinus implant is a corticosteroid-eluting implant indicated for the treatment of (b) (4) polyps, in patients >=18 years of age who have had ethmoid sinus surgery.

**NDA:** 209310

**Drug Product Name / Strength:** Mometasone Furoate Sinus Implant (1350mcg)

**Route of Administration:** Sino-nasal

**Applicant Name:** Intersect ENT, Inc.

**Review Summary:**

Following review of the inspection documentation and application documents, the manufacturing facilities for NDA 209310 are **acceptable**.

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

| Reviewed Submissions | | |
|---|---|---|
| Description | SD # (Sequence) | Date |
| Original Submission | 1 (0001) | 7-MAR-2017 |
| Response to Process IR | 11 (0011) | 5-SEP-2017 |

**Highlight Key Outstanding Issues from Last Cycle:** N/A

**Concise Description Outstanding Issues Remaining:** N/A

## 3.2.S.2 Manufacture

**Summary of Facility Information:**

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(b) (4)

[redacted]

***Comparability Protocols***

**Reviewer's Assessment: N/A**

***Post-Approval Commitments***

**Reviewer's Assessment: N/A**

***Lifecycle Management Considerations***

N/A

***List of Deficiencies: N/A***

***Primary Facilities Reviewer Name and Date:***

*Daniel DeCiero, Chemical Engineer OPQ/OPF/DIA/IABII, 11/29/2017*

***Secondary Reviewer Name and Date:***

*Derek Smith, 11/29/2017*

Derek Smith

Digitally signed by Derek Smith
Date: 11/29/2017 03:44:18PM
GUID: 508da7480002bfe5d5fe14a12da3599d

Daniel DeCiero

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Date: 11/30/2017 08:59:27AM
GUID: 55ba359e00a34e89af5c3ed97f25e415

# LABELING

## I. Package Insert

### 1. *Highlights of Prescribing Information*

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use *PROPRIETARY NAME* safely and effectively. See full prescribing information for <*PROPRIETARY NAME*>.**

**PROPRIETARY NAME (mometasone furoate) sinus implant (b) (4)**
**Initial U.S. Approval: YYYY**

---------- **INDICATIONS AND USAGE**----------
<*PROPRIETARY NAME*> Sinus Implant (b) (4) is a (b) (4) polyps, in patients ≥ 18 years of age who have had ethmoid sinus surgery. (1)
----------**DOSAGE AND ADMINISTRATION**----------
The <*PROPRIETARY NAME*> Sinus Implant is loaded into a delivery system and placed in the ethmoid sinus under endoscopic visualization. The Implant may be left in the sinus to gradually release the corticosteroid over 90 days, based on preclinical data. The Implant can be removed earlier at the physician's discretion, using standard surgical instruments. (2.2)
----------**DOSAGE FORM AND STRENGTH** ----------
Dosage consists of one <*PROPRIETARY NAME*> Sinus Implant containing 1350 mcg of mometasone furoate. (3)

Sinuva (mometasone furoate) sinus implant~~,~~ (b) (4) ~~)~~

***Reviewer Notes***: (b) (4) the established name. The applicant should ensure that the established name is consistent throughout the package insert – some places they have (b) (4) included in the established name and in other places they do not.

| Item | Information Provided in NDA |
|---|---|
| Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2)) | |
| Proprietary name and established name | X (provided, but should be made consistent throughout PI) |
| Dosage form, route of administration | X |
| Controlled drug substance symbol (if applicable) | N/A |
| Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8)) | |
| Summary of the dosage form and strength | X |

## 2. *Section 2 Dosage and Administration*

### 2.1 Dosing

Dosage consists of one <*PROPRIETARY NAME*> Sinus Implant containing 1350 mcg of mometasone furoate.

### 2.2 General Instructions

The <*PROPRIETARY NAME*> Sinus Implant (Figure 1) is loaded into a delivery system and placed in the ethmoid sinus under endoscopic visualization. The <*PROPRIETARY NAME*> Sinus Implant is made from bioabsorbable polymers designed to gradually soften over time. The Implant may be left in the sinus to gradually release the corticosteroid over 90 days, based on preclinical data. The Implant can be removed earlier at the physician's discretion, using standard surgical instruments.

### 2.3 Health Care Provider Training

The Sinuva Sinus Implant is to be used by physicians trained in otolaryngology. Specialized training is not required for these physicians.

(b) (4)

### 2.5 Placement of <PROPRIETARY NAME> Implant

The <*PROPRIETARY NAME*> Sinus Implant is designed for single patient use only. Do not reprocess or reuse.

- Do not use if the package is open or the package or product is damaged or has evidence of gross contamination.
- Special care should be taken to avoid bending, twisting or damaging the implant.
- The implant is not designed to be modified by the physician.
- The implant is not intended to be compressed and loaded into the delivery system more than two times. The implant must be placed under endoscopic visualization.

### Patient Preparation

The patient should be prepared following routine protocols for in-office sinonasal endoscopic procedures. (b) (4)

(b) (4)

### Implant Preparation

Remove the Crimper (Figure 2) and the Delivery System (Figure 3) from their protective packaging using sterile technique. Inspect the <*PROPRIETARY NAME*> Sinus Implant

located inside of the Crimper (Figure 2). Do not remove the Implant from the Crimper. Prior to use, the <*PROPRIETARY NAME*> Sinus Implant must be crimped and loaded into the Delivery System. If the <*PROPRIETARY NAME*> Sinus Implant is not fully seated inside of the Crimper, secure the <*PROPRIETARY NAME*> Sinus Implant before proceeding. See instructions to secure the <*PROPRIETARY NAME*> Sinus Implant (Figure 12 & Figure 13).

**IMPLANT**
Length (nominal): 20 mm
Expanded Diameter (nominal): 34 mm
**DELIVERY SYSTEM** Shaft Length 117 mm

1. Place the Crimper on a flat surface and hold to prevent any potential slipping of the Crimper during loading of the <*PROPRIETARY NAME*> Sinus Implant into the Delivery System. Orient the crimper such that the short ends of the Implant are in the 12 o'clock and 6 o'clock position (Figure 4)

2. Grasp the Delivery System with the index and middle fingers using the Finger Rests and the thumb in the Thumb Rest (Figure 5).

3. Pull back on the Finger Rests while pressing down on the Thumb Rest to retract the Cup, and expose the Seeker (Figure 6).

4. Position the tip of the Seeker with 10° angled tip downwards toward the user in the depression in the center of the <*PROPRIETARY NAME*> Sinus Implant (Figure 7). The distal end of the angled shaft must be in a vertical position, perpendicular to the Crimper, during positioning. Ensure the plane of the angled tip is in the same plane as the short ends of the Implant that were oriented in the 12 o'clock / 6 o'clock position in step 1.

5. With the Thumb Rest depressed, gradually apply perpendicular downward force to the <*PROPRIETARY NAME*> Sinus Implant until the ends of the Implant collapse around the Seeker of Delivery System (Figure 8). Make sure that the Finger Rests are not released while pushing downwards.

6. The <*PROPRIETARY NAME*> Sinus Implant should crimp in a radial fashion onto the Seeker. Implant ends should not cross over or past each other when being crimped onto the Seeker by the Crimper.

7. While maintaining steady downward pressure on the Thumb Rests, slowly release the Finger Rests with the index and middle fingers until the Cup lowers and captures all ends of the <*PROPRIETARY NAME*> Sinus Implant. If necessary, adjust the position of the Delivery System with slight circular movements, slightly lifting and then lowering the Cup into position to ensure that all eight ends of the <*PROPRIETARY NAME*> Sinus Implant are secured within the Cup.

8. Apply a gentle downward push on the Delivery System to ensure that the <*PROPRIETARY NAME*> Sinus Implant is secured in the Cup. This will also ensure the implant is compressed to its smallest profile for insertion.

9. Retract the Delivery System from the Crimper. The <*PROPRIETARY NAME*> Sinus Implant should remain symmetrically loaded in the Cup of the Delivery System (Figure 9).

**CAUTION: Do not leave the <*PROPRIETARY NAME*> Sinus Implant in the crimped state for more than 5 minutes prior to placement.**

**Instructions to Secure the <*PROPRIETARY NAME*> Sinus Implant in the Crimper**
If necessary, the implant may be reloaded into the crimper for a second time.
**CAUTION: The <*PROPRIETARY NAME*> Sinus Implant should not be used if the second attempt to crimp is unsuccessful.**

1. Hold the <*PROPRIETARY NAME*> Sinus Implant by one end as shown in Figure 10.

2. Holding the <*PROPRIETARY NAME*> Sinus Implant with the dome-shaped cap positioned downward (Figure 11), place the Implant back into the crimper.

3. Ensure that each implant is secured in the Crimper by pressing down on the center of the Implant until all ends of the Implant are below the Crimper Cap (Figure 12).

4. Inspect the Implant and the Crimper to ensure that all the Implant ends are secured below the Crimper Cap (Figure 13).

**Instruction for the <*PROPRIETARY NAME*> Sinus Implant Placement**
Advance the Delivery System under endoscopic visualization into the ethmoid sinus cavity.

1. Ensure that the Delivery System is oriented such that the 10° curvature of the distal tip is curved superiorly. Insert the Delivery System such that the Shaft is parallel to roof of ethmoid sinus.

2. If the <*PROPRIETARY NAME*> Sinus Implant becomes dislodged from the Delivery System prior to placement into the ethmoid sinus, remove the Implant and inspect for damage, re-load the undamaged Implant in the Crimper and re-crimp the Implant into the Delivery System. Note that the <*PROPRIETARY NAME*> Sinus Implant should not be loaded into the Delivery System more than twice.

3. Release the <*PROPRIETARY NAME*> Sinus Implant by pressing down on the Thumb Rest while pulling back on the Finger Rests in a controlled manner.

4. Place the <*PROPRIETARY NAME*> Sinus Implant amongst the sinus polyps with the cap oriented toward the posterior ethmoid sinus, and with the Implant positioned as

superiorly as possible in the sinus. The long ends of the implant should be in approximately the 2 o'clock, 4 o'clock, 8 o'clock and 10 o'clock positions, respectively. Confirm final placement of the <*PROPRIETARY NAME*> Sinus Implant by endoscopic visualization. To adjust the position of the <*PROPRIETARY NAME*> Sinus Implant, use the Seeker on the Delivery System or standard endoscopic surgical instruments.

**Post Placement Instructions**
Reposition the Implant if its ends are perpendicular to and in contact with the nasal septum. Avoid excessive manipulation of the Implant during follow-up as it can cause dislodgement.

**2.6 Removal Instructions**
The <*PROPRIETARY NAME*> Sinus Implant is made from bioabsorbable polymers designed to gradually soften over time. The Implant may be left in the sinus to gradually release the corticosteroid over 90 days, based on preclinical data. The <*PROPRIETARY NAME*> Sinus Implant can be removed at any time at the physician's discretion using standard endoscopic instruments.

(b) (4)

***Reviewer Notes***: The figures referenced above were not copied into this review (see package insert).

| Item | Information Provided in NDA |
|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(12)) | |
| Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents) | X |

### 3. *Section 3 Dosage Forms and Strengths*

Each <*PROPRIETARY NAME*> Sinus Implant is a sterile, single-use, (b) (4) bioabsorbable (b) (4) implant, coated with a formulation containing 1350 mcg mometasonefuroate that is gradually released over 90 days (b) (4)

| Item | Information Provided in NDA |
|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(4)) | |
| Available dosage forms | X |
| Strengths: in metric system | X |
| Active moiety expression of strength with equivalence statement (if applicable) | X |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable. | N/A – clinical division stated that identifying characteristics should be in Section 11, not Section 3 |

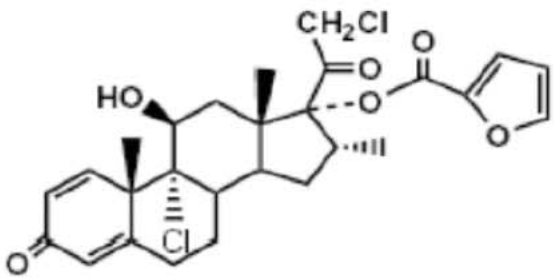
**4. *Section 11 Description***

The <*PROPRIETARY NAME*> Sinus Implant is a self-expanding, bioabsorbable, drug eluting implant provided with a crimper and a single-use delivery system. <*PROPRIETARY NAME*> is comprised of poly(L-lactide-co-glycolide) and poly(L-lactide-co-ε-caprolactone) coated with mometasone furoate embedded in a bioabsorbable polymer matrix containing poly(DL-lactide-co-glycolide) and polyethylene glycol (inactive ingredients) which provides for gradual release of the drug. (b) (4) The <PROPRIETARY NAME> Sinus Implant is packaged in a tray, which is then sealed in a foil pouch and placed in the product carton. The <*PROPRIETARY NAME*> product is provided sterile.

Mometasone furoate, the active component of the <*PROPRIETARY NAME*> Sinus Implant, is a corticosteroid with the chemical name 9,21-dichloro-11(Beta),17-dihydroxy-16(alpha)- methylpregna-1,4-diene-3,20-dione 17 (2-furoate). Mometasone furoate is a white powder with an empirical formula of C27H30Cl2O6, and molecular weight of 521.44 Daltons.

***Reviewer Notes***: The sentence "The implant exhibits no antimicrobial properties" does not seem necessary. 'Beta' and 'alpha' should be converted to symbols. The chemical formula should contain subscripted numbers.

The chemical structure of mometasone furoate is shown below:



The inactive ingredients are poly-(DL-lactide-co-glycolide) and polyethylene glycol. Poly-(DL-lactide-co-glycolide) is an amorphous biodegradable polymer. (b) (4)

(b) (4)

***Reviewer Notes***: (b) (4)

| Item | Information Provided in NDA |
|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)) | |
| Proprietary name and established name | X |
| Dosage form and route of administration | X |
| Active moiety expression of strength with equivalence statement (if applicable) | X |
| For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>) | N/A |
| Statement of being sterile (if applicable) | X |
| Pharmacological/ therapeutic class | X |
| Chemical name, structural formula, molecular weight | X |
| If radioactive, statement of important nuclear characteristics. | N/A |
| Other important chemical or physical properties (such as pKa or pH) | X |

### 5. *Section 16 How Supplied/Storage and Handling*

One <*PROPRIETARY NAME*> Sinus Implant kit consists of an individual implant inside of a crimper and one ~~D~~disposable delivery system packaged in a foil pouch. The <*PROPRIETARY NAME*> Sinus Implant is 20 mm in length and 34 mm in expanded diameter (Figure 1) and contains 1350 mcg of mometasone furoate.
Store the <*PROPRIETARY NAME*> Sinus Implant at 20–25°C (68–77°F); excursions permitted at 15–30°C (59–86°F) [*see USP Controlled Room Temperature*].

(b) (4)

***Reviewer Notes***: Corrections to some formatting and typographical errors were made above. Also, the last paragraph is not needed.

The NDC code for the <*PROPRIETARY NAME*> Sinus Implant is #####-###-##.

| Item | Information Provided in NDA |
|---|---|
| (Refer to Labeling Review Tool and 21 CFR 201.57(c)(17)) | |
| Strength of dosage form | X |
| Available units (e.g., bottles of 100 tablets) | X |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | X |
| Special handling (e.g., protect from light) | N/A |
| Storage conditions | X |
| Manufacturer/distributor name (21 CFR 201.1(h)(5)) | X |

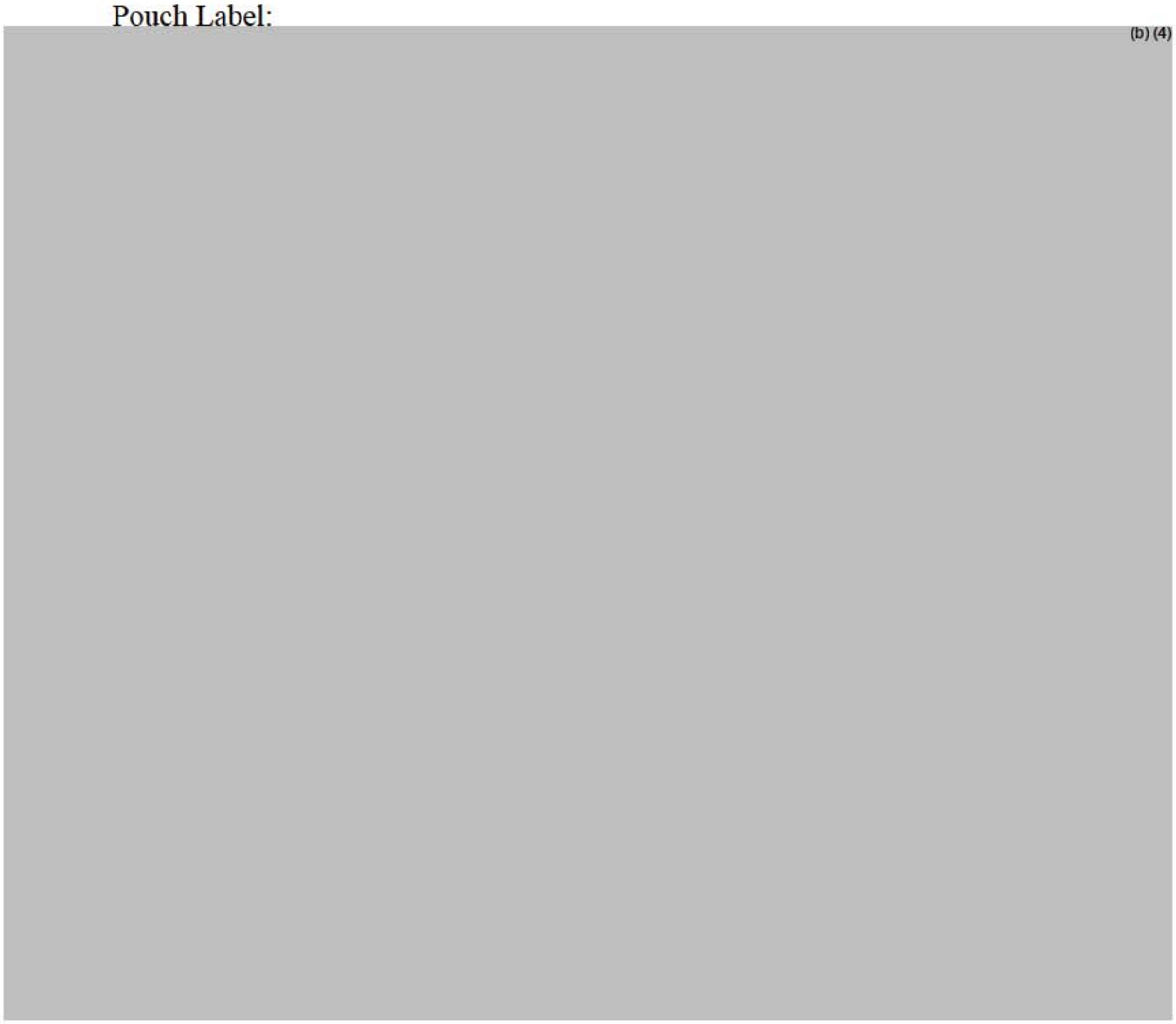
**Reviewer's Assessment of the Package Insert**: **ADEQUATE**. The revisions to the Package Insert noted above were conveyed to the clinical division on 24-Oct-2017 via interactive mark-up of the labeling. The revised package insert will be sent to the applicant and finalized through continuing interactive mark-up until agreement has been reached between the Agency and the applicant. With the noted changes, the labeling information complies with all regulatory requirements from a CMC perspective.

## II. Labels:

### 1. *Container and Carton Labels*

Pouch Label:

(b) (4)



**2. *Carton Label***

Labeled Shelf Carton:

| Item | Information provided in the container label | Information provided in the carton label(s) |
|---|---|---|
| Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2)) | X (to be revised) | X (to be revised) |
| Dosage strength | X | X |
| Net contents | | |
| "Rx only" displayed prominently on the main panel | X | X |
| NDC number (21 CFR 207.35(b)(3)(i)) | X | X |
| Lot number and expiration date (21 CFR 201.17) | X | X |
| Storage conditions | X (to be revised) | X (to be revised) |
| Bar code (21CFR 201.25) | X | X |
| Name of manufacturer/distributor | X | X |
| And others, if space is available | N/A | N/A |

**Reviewer's Assessment of Labels: ADEQUATE**. With the revisions noted above, the labels will comply with all regulatory requirements from a CMC perspective. The revisions will be conveyed to the applicant during interactive review of the labels.

**Review Recommendation:**
Based on material provided by the Applicant, approval of this NDA is recommended from a CMC labeling perspective.

***Primary Drug Substance Reviewer Name and Date:***

Monica D. Cooper, Ph.D.
Review Chemist
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
02-Nov-2017

***Secondary Reviewer Name and Date:***

Concurrence: I concur with the recommendation of the primary labeling reviewer.

Benjamin D. Stevens, Ph. D., M.P.H.
Acting Branch Chief
FDA/CDER/OPQ/ONDP/New Drug API Branch 1
02-Nov-2017

Monica Cooper

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Date: 11/02/2017 08:56:41PM
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Ben Stevens

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Date: 11/03/2017 07:24:03AM
GUID: 5432b4d800086115752a874a47534532

# OFFICE OF PHARMACEUTICAL QUALITY

## Attachment – Final Risk Assessment

| DP attribute/ CQA | Factors that can impact the CQA | O[1] | S[1, 2] | D[1] | FMECA RPN # | Comment & considerations |
|---|---|---|---|---|---|---|
| Appearance | • broken device struts<br>• cracked cap<br>• missing struts<br>• visible contamination | 3[3] | 3 | 2 | 18 | • Visual examination performed for batch release<br>• Applicant states that a (b) (4)% final inspection is completed prior to packaging |
| Identification | • incorrect API formulated<br>• no API formulated | 1 | 3 | 1 | 3 | • Adherence to cGMPs should mitigate these factors<br>• (b) (4) |
| Assay, impurities/ degradation products | (b) (4) | | | | | |
| Residual solvent (b) (4) | • | | | | | (b) (4) |

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability

[2] Severity of effect can only be estimated; input from clinical or pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs; beyond the scope of a CMC risk assessment.

[3] The probability of occurrence of will need to be assessed by CDRH, as these factors are all device-related

# OFFICE OF PHARMACEUTICAL QUALITY

## Attachment – Final Risk Assessment

| | (b) (4) | | | | | (b) (4) |
|---|---|---|---|---|---|---|
| | | | | | | |
| Uniformity of dosage units | | 2 | 3 | 2 | 12 | |
| Sterility[4] | | | 3 | | | |
| Drug Release or Dissolution | | 2 | 3 | 2 | 12 | |

[4] Evaluated by the microbiology team; (b) (4)

Craig Bertha

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Date: 11/30/2017 11:03:39AM
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**DEPARTMENT OF HEALTH & HUMAN SERVICES**
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)
Division of Manufacturing and Quality (DMQ)

# ICCR QUALITY SYSTEM REVIEW CHECKLIST

| | |
|---|---|
| **Date:** | June 15, 2017 |
| **To:** | ICCR Lead-Center Contact, Office, Location, E-mail:<br>Bamidele Aisida, OPQ/ONDP, Bamidele.Aisida@fda.hhs.gov<br>Craig Bertha, OPQ/ONDP, Craig.Bertha@fda.hhs.gov |
| **CC:** | Office of Combination Product at: combination@fda.gov<br><br>Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM):<br>Craig Bertha, OPQ/ONDP, Craig.Bertha@fda.hhs.gov<br>CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov |
| **Through:** | Jamie Kamon-Brancazio, REGO/DMQ/OC, CDRH, WO 66, Rm 3427, E-mail: Jamie.Kamon-Brancazio@fda.hhs.gov |
| **From:** | Susannah Gilbert, REGO/DMQ/OC, CDRH, WO 66, Rm 3431, E-mail: Susannah.Gilbert@fda.hhs.gov |
| **Applicant/Licensure:** | Intersect Ent Inc.<br>1555 Adams Dr.<br>Menlo Park CA 94025<br>FEI: 3008301917 |
| **Submission (Type & Number):** | NDA209310 |
| **Combination Product Name:** | S8 Sinus Implant |
| **Combination Product** | Drug coated biodegradable implant |
| **Intended Use:** | Treatment of sino-nasal symptoms associated with sinus obstruction. |
| **Device Constituent (Type):** | Drug coated biodegradable implant |
| **ICCR Number:** | ICCR1700221 |
| **ICCR Instruction (ICCR Form):** | Facilities inspection consults for a CDER application (e.g. identifying the need for pre-market inspection of facilities for non-lead center constituent parts) to CDRH |
| **Pre-Approval Facility Inspection:** | **No** |
| **Documentation Review (Status):** | **Complete, Information - Adequate** |
| **CDRH/OC Recommendation:** | **Approvable** |

The Office of Compliance at CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA 209310 which will require a device inspection.

## PRODUCT DESCRIPTION

The subject product, the S8 Sinus Implant, is a combination product (drug-device) comprised of a bioabsorbable self-expanding dug-eluting sinus stent (implant) coated with 1350mcg of Mometasone Furoate (MF). This sino-nasal implant, which elutes a corticosteroid, is used to treat (b) (4) polyps, in adult patients who have had ethmoid sinus surgery. The product is provided with a single-use crimper and single-use delivery system.

The S8 Sinus Implant is designed to provide controlled release of drug to the mucosal tissue, and is designed with sufficient mechanical strength to improve obstruction in the ethmoid sinus.

The implant is manufactured from (b) (4) bioabsorbable copolymers that are formed to provide a rounded cap at the leading end and arched components that expand after placement (as seen in **Figure 1** below). The implant is (b) (4) coated with a coating that contains bioabsorbable polymer carriers and the mometasone furoate drug. The implant is provided with a single use crimping tool (**Figure 2**) that is used to compress the implant and load it into the included single use delivery system (**Figure 3**).

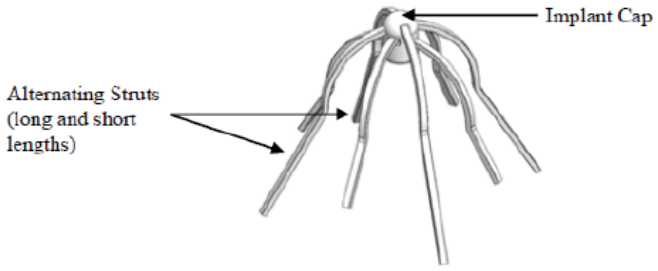


**Figure 1: S8 Sinus Implant**

**Figure 2: Crimper with Implant**

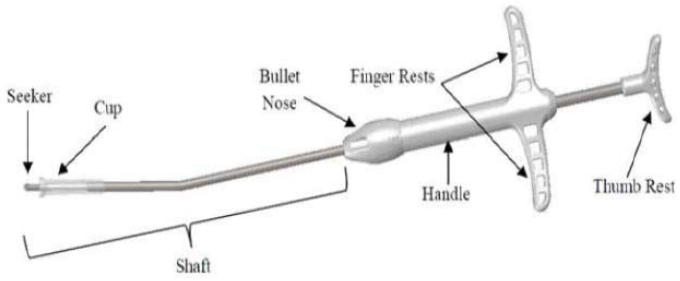


**Figure 3: Delivery System**

## REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the S8 Sinus Implant in NDA209310.

Intersect ENT Inc.
1555 Adams Dr.
Menlo Park CA 94025
FEI: 3008301917

Inspectional History: An analysis of the firm's inspection history over the past 2 years showed that inspections were conducted 04/04/2017 to 04/06/2017, and 06/23/2014 to 06/27/2014. These inspections covered the Management Controls, Corrective and Preventive Action (CAPA) Controls, and Production and Process Controls (P&PC) subsystems; and focused on Intersect ENTs latest device in US distribution: the Propel Contour and delivery system. These inspections were classified NAI.

## INSPECTION RECOMMENDATION:

An inspection **is not required** because the recent medical device inspection of the firm was acceptable.

## DOCUMENTATION REVIEW

| | | | |
|---|---|---|---|
| 1. Was the last inspection OAI for drug or device observations? | YES ☐ | NO ☒ | NA ☐ |
| 2. Is the device constituent a PMA or class III device? | YES ☐ | NO ☒ | UNK ☐ |
| 3. Is the final combination product meant for emergency use? | YES ☐ | NO ☒ | UNK ☐ |
| 4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or imimmunocompromised patients)? | YES ☐ | NO ☒ | UNK ☐ |
| 5. Does the manufacturing site have a known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes? | YES ☐ | NO ☒ | UNK ☐ |
| 6. Would withholding approval of the finished combination product create a shortage? | YES ☐ | NO ☒ | UNK ☐ |

**cGMP Risk:** ☒ Low or Moderate Risk of cGMP issues: If yes is not checked above, please continue the checklist.

☐ High Risk of cGMP issues: If yes is checked anywhere above, consider conducting a full ICCR review and issuing inspections based on a facilities review. If a full review and preapproval inspections are not warranted due to other factors such as device constituent classification, a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review to continue to use the checklist.

*Reviewer Comments: A previous version of the implant was approved in P100044. Although this previous version was a PMA product, both the dosage and the product design have changed for this NDA. Despite these differences, the drug distribution*

*mechanism and risk have been previously assessed with the prior approval, and therefore the risk associated with the review of this drug product is decreased.*

| | | | |
|---|---|---|---|
| 7. Was the last inspection VAI for drug or device observations? | YES ☐ | NO ☒ | NA ☐ |
| 8. Has the firm not had any previous device inspections? | YES ☐ | NO ☒ | UNK ☐ |
| 9. Is the combination product meant for home use, hospital use, or military use? | YES ☐ | NO ☒ | UNK ☐ |
| 10. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)? | YES ☐ | NO ☒ | UNK ☐ |
| 11. Does the firm have a known history of class II device recalls, MDRs/AEs, or VAI inspections? | YES ☐ | NO ☒ | NA ☐ |

**cGMP Risk:** ☒ Low Risk of cGMP issues: If yes is not checked above, please continue the checklist.

☐ Moderate Risk of cGMP issues: If yes is checked anywhere above, consider conducting a full ICCR review and issuing inspections based on a facilities review. If a full review and preapproval inspections are not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review to continue to use the checklist.

*Reviewer Comments: The combination product is an implant that is inserted in a physician's office setting.*

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the quality system requirements applicable to the entire manufacturing process and across all facilities.

**Manufacturing Site:** Intersect ENT Inc.
1555 Adams Dr.
Menlo Park CA 94025
FEI: 3008301917

| | | | |
|---|---|---|---|
| **Management Responsibility, 21 CFR 820.20**<br>The firm provided a summary of how the firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). | YES ☒ | NO ☐ | NA ☐ |
| The firm provided a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts. | YES ☒ | NO ☐ | NA ☐ |
| **Design Controls, General, 21 CFR 820.30**<br>The firm explained how it utilized the design control process to develop the combination product under review and provided a description of its design control procedures. | YES ☒ | NO ☐ | NA ☐ |
| The firm provided a copy or a summary of the plan used to design the combination product. | YES ☒ | NO ☐ | NA ☐ |
| **Purchasing Controls, 21 CFR 820.50**<br>The sponsor firm should summarize its procedure(s) for purchasing controls. | YES ☒ | NO ☐ | NA ☐ |
| The summary should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers. | YES ☒ | NO ☐ | NA ☐ |
| The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process. | YES ☒ | NO ☐ | NA ☐ |
| The summary should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use. | YES ☒ | NO ☐ | NA ☐ |
| The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product. | YES ☒ | NO ☐ | NA ☐ |
| The firm should provide a description of how it applied the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement). | YES ☒ | NO ☐ | NA ☐ |
| **Corrective and Preventive Action (CAPA), 21 CFR 820.100**<br>The sponsor firm should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System. | YES ☒ | NO ☐ | NA ☐ |

| | | | |
|---|---|---|---|
| The CAPA system should require:<br>a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products; | YES ☒ | NO ☐ | NA ☐ |
| b. Investigation of nonconformities and their causes; | YES ☒ | NO ☐ | NA ☐ |
| c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and | YES ☒ | NO ☐ | NA ☐ |
| d. Verification or validation of the actions taken. | YES ☒ | NO ☐ | NA ☐ |
| **Installation, 21 CFR 820.170 (check NA if Installation is not required for the combination product)**<br>If applicable for the combination product, the firm should provide a summary of how it has established installation, inspection instructions, and test procedures for the installation of the combination product. | YES ☐ | NO ☐ | NA ☒ |
| **Servicing, 21 CFR 820.200 (check NA if Servicing is not required for the combination product)**<br>Where servicing is a specified requirement for the combination product, the firm should provide a summary of how it has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements. | YES ☐ | NO ☐ | NA ☒ |

**Documentation Review Recommendation:** The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable quality system requirements showed no deficiencies. No additional information is required for the documentation review.

Based on the firm's history of device manufacturing, the recent site inspection, and the low risk associated with this device, we recommend approval despite minimal information regarding processes associated with design changes.

We recommend approval, and that upon routine inspection, that the purchasing controls are verified.

## RECOMMENDATION

The application for the S8 Sinus Implant NDA209310 is approvable from the perspective of the applicable Quality System Requirements.

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

**OC Decision:** ☒ Approvable (Recommend approval to CDER)

☐ Withold (Issue Device Quality System Deficiencies to CDER or Recommend Inspections)

☐ Not Approvable

**Reviewer:** Susannah Gilbert -S
2017.06.16 09:58:48 -04'00'

**Branch Chief or Lead CSO:** Jamie Kamon-brancazio -A
Digitally signed by Jamie Kamon-brancazio -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001568505, cn=Jamie Kamon-brancazio -A
Date: 2017.07.07 08:14:48 -04'00'