# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 213426Orig1s000

# PRODUCT QUALITY REVIEW(S)

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

# RECOMMENDATION

| |
|---|
| ☒ Approval |
| ☐ Approval with Post-Marketing Commitment |
| ☐ Complete Response |

# NDA 213426
# Assessment # 2

| | |
|---|---|
| **Drug Product Name** | Celecoxib and Tramadol hydrochloride, Tablets |
| **Dosage Form** | Tablet |
| **Strength** | 56 mg celecoxib and 44 mg tramadol HCl |
| **Route of Administration** | oral |
| **Rx/OTC Dispensed** | Rx |
| **Applicant** | Esteve Pharmaceuticals, S.A. |
| **US agent, if applicable** | Rebecca Nortz, c/o Esteve Pharmaceuticals, LLC |

| Submission(s) Assessed | Document Date | Discipline(s) Affected |
|---|---|---|
| 0027 (27) Submission after complete response | 04/16/2021 | Drug Product, Drug Substance, OPMA |
| 0028(28) IR response | 06/01/2021 | Drug substance |

**QUALITY ASSESSMENT TEAM**

| Discipline | Primary Assessment | Secondary Assessment |
|---|---|---|
| **Drug Substance** | Sukhamaya Bian | Donna Christner |
| **Drug Product** | Renishkumar Delvadia | Julia Pinto |
| **Manufacturing** | Tarun Mehta | Ubrani Venkataram<br><br>Jonathan Swoboda |
| **Microbiology** | N/A | N/A |
| **Biopharmaceutics** | N/A | N/A |
| **Regulatory Business Process Manager** | Anika Lalmansingh | |

| | | |
|---|---|---|
| **Application Technical Lead** | Renishkumar Delvadia | |
| **Laboratory (OTR)** | N/A | |
| **Environmental** | N/A | |

# EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

*This application is recommended for approval by OPMA. In the last review cycle, (b) (4) (FEI: (b) (4)), the manufacturer (b) (4) was not ready for inspection, which led to issuance of the Complete Response letter. In the resubmission package, the applicant has withdrawn (b) (4) (b) (4) (b) (4) (FEI: (b) (4)). Based on inspection history and compliance, the subject application is recommended for approval from a facility perspective. The Application also remains approvable from drug substance, biopharmaceutics, and drug product perspective.*

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

The proposed drug product is a white to off-white, elongated coated tablet, debossed with "100" on one side and "CTC" on the other side. The tablets contain 100 mg of co-crystal containing 56 mg of celecoxib and 44 mg of tramadol hydrochloride. The coated tablets will be packaged in white, opaque high-density polyethylene (HDPE) bottles with (b) (4) child resistant screw-cap and tamper evidence (b) (4) (b) (4) The 30-count configuration will be filled in 35-mL bottles and the 90-count configuration will be filled in 50-mL bottle

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | For the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. |
| **Duration of Treatment** | |

| | |
|---|---|
| **Maximum Daily Dose** | The Maximum daily dose is 400 mg of co-crystal equivalent to 224 mg of Celecoxib and 176 mg of Tramadol HCl. |
| **Alternative Methods of Administration** | N/A |

## B. Quality Assessment Overview

**Drug Substance: Adequate**

The drug substance information remains adequate from the CMC perspective, and the NDA also remains recommended for approval from the drug substance perspective. Note that the Complete Response letter did not have any drug substance CMC issue, and the NDA was recommended for approval from the drug substance perspective in the last review cycle. The resubmission does not include any drug substance CMC, except for the updated stability information. The referenced DMFs (b) (4) were reviewed for changes in the drug substance information and found adequate.

**Drug Product: Adequate**

The NDA remains recommended for approval from the drug product perspective. In the last review cycle, there were NO outstanding deficiencies from the drug product perspective. In the resubmission, the Applicant has submitted additional long-term registration stability data (24-month and 36-month timepoints) for the three registration stability batches and revised the proposed shelf-life to 36 months. No new stability trend or out-of-specification (OOS) results are observed during 36 months of long-term storage. The additional long-term stability data provided in the resubmission support extension of the proposed shelf-life from 24 months to 36 months. In addition to the stability data, the Applicant has informed that the name of the drug product manufacturing site has been changed from Esteve Pharmaceuticals, S.A. to Towa Pharmaceutical Europe, S.L., and the name of the supplier (b) (4) (b) (4) has been changed (b) (4)

**Labeling: Adequate**

The labeling was deemed adequate in the first review cycle from the CMC perspective, and remains adequate in the current review cycle.

**Manufacturing: Adequate**

During the first review cycle, the (b) (4) manufacturing site ( (b) (4) FEI: (b) (4) ) was not ready for inspection supporting the initial withhold

recommendation. During the Second Cycle review, the applicant has withdrawn (b) (4) (FEI: (b) (4)) as a (b) (4) manufacturing facility (b) (4) (FEI: (b) (4)). Additionally, in this review cycle, the applicant has added the testing site (b) (4) (b) (4) Based on inspection history and compliance, the subject application is recommended for approval from a facility perspective. No changes are noted for the process assessment; therefore, the assessment remains recommended for approval. Note that the Applicant has informed that the name of the drug product manufacturing site has been changed from Esteve Pharmaceuticals, S.A. to Towa Pharmaceutical Europe, S.L

Facilities table:

| Facility name and address | FEI | Responsibilities and profile code(s) | Status |
|---|---|---|---|
| (b) (4) | (b) (4) | Manufacturing, quality control testing, stability testing, packaging, batch release and storage of the drug substance. \|\| DMF: (b) (4) \|\| 356h (b) (4) | Approve - Based on Previous History |
| | | Testing (b) (4) for the batch release of the drug substance. \|\| DMF: (b) (4) \|\| 356h Status: LCP | Approve - Based on Previous History |
| | | Manufacturing and testing of Celecoxib (b) (4) (b) (4) \|\| DMF: (b) (4) \|\| 356h Status: (b) (4) | Approve - Based on Previous History |
| | | Manufacturing and testing of Tramadol HCl \|\| DMF: (b) (4) \|\| 356h Status: (b) (4) | Approve - Based on Previous History |
| | | Manufacturing and testing (b) (4) (b) (4) \|\| 356h Status: (b) (4) | Approve - Based on Previous History |

| | | | |
|---|---|---|---|
| | | (b) (4) Second Cycle Review added as manufacturer (b) (4) (b) (4) | |
| | | Manufacturing and testing (b) (b) (4) \|\| 356h Status: (b) (4) Withdrawn in second cycle review | Withdrawn |
| | | Manufacturing and testing (b) (b) (4) \|\| 356h Status: (b) (4) | Withdrawn |
| | | Celecoxib (b) (4) release testing \|\| 356h Status: PendingCelecoxib (b) (4) release testing \|\| 356h Status: Pending LCP | Approve - Based on Previous History |
| Esteve Pharmaceuticals, S.A.Esteve Pharmaceuticals, S.A. (Now called Towa Pharmaceutical Europe, S.L. per Attachment to Form 356h submitted in eCTD#0027)) C/ de Sant Martí, 75-97 , Martorelles, Barcelona, Spain, 8107C/ de Sant Martí, 75-97 , Martorelles, Barcelona, Spain, 8107 | 3003121577 | Drug product manufacturer for Celecoxib and Tramadol, Tablets. Responsible for manufacturing, packaging, labeling, release testing (drug product and components) and stability testing. \|\| 356h Status: TCM | Approve - Based on Previous History |
| | (b) (4) | (b) (4) Testing of Celecoxib-Tramadol, co-crystal API (drug substance). \|\| 356h Status: Pending (b) (4) Testing of Celecoxib-Tramadol, co-crystal API (drug substance). \|\| 356h Status: Pending LCP | Approve - Based on Previous History |
| | | Testing of USP/NF excipients used in drug product manufacture of Celecoxib and Tramadol, Tablets \|\| 356h Status: PendingTesting of USP/NF excipients used in drug product manufacture of Celecoxib and Tramadol, Tablets \|\| 356h Status: Pending | No Evaluation Necessary |

| | | |
|---|---|---|
| (b) (4) | LCP | |
| | Testing site for (b) (4) Tramadol HCl<br><br>LCP | Approve - Based on Previous History |

**Biopharmaceutics: Adequate**

The Complete Response letter did not have any biopharmaceutics issues, and the NDA was recommended for approval from the biopharmaceutics perspective. No new biopharmaceutics information has been submitted in the resubmission, except for the stability data; stability data are reviewed by the drug product reviewer. Therefore, separate biopharmaceutics review is not necessary. The NDA remains recommended for approval from the biopharmaceutics perspective.

## C. Risk Assessment (No change since the last review cycle)

| From Initial Risk Identification | | | Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking** | **Risk Mitigation Approach** | **Final Risk Evaluation** | **Lifecycle Considerations/ Comments** |
| Assay, Stability | Formulation<br>• Container closure<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | (b) (4) | Acceptable | None |
| Physical stability (solid state) | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site<br>• | M | | Acceptable | None |
| Content uniformity | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | | Not Acceptable | See manufacturing deficiencies. |

| | | | | | |
|---|---|---|---|---|---|
| Microbial limits | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | L | (b) (4) | Acceptable | |
| Dissolution | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | | Acceptable | |

## D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

# QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

## 1. RELATED/SUPPORTING DOCUMENTS

**A. DMFs:**

| DMF # | Type | Holder | Item Referenced | Status | Date Assessment Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | II | | (b) (4) | Active | 06/29/2021 (reviewed by Dr. Sukhamaya Bai) | Adequate |
| | II | | | Active | 06/23/2021 (reviewed by Dr. Sukhamaya Bai) | Adequate |
| | II | | | Active | 06/22/2021 (reviewed by Dr. Sukhamaya Bai) | Adequate |
| | III | | | Active | N/A | Sufficient information in NDA application |
| | IV | | | Active | N/A | Sufficient information in NDA application |

**B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA***

| Document | Application Number | Description |
|---|---|---|
| NDA | 02028 | Ultram, Janseem Pharms |
| NDA | 021692 | Ultram ER, Valeant Pharms |
| NDA | 020998 | Celebrex, GD Searle |
| IND | 128177 | Co-crystal E-58425, LABORATORIOS DEL DR ESTEVE SA |

## 2. CONSULTS

| Discipline | Status | Recommendation | Date | Assessor |
|---|---|---|---|---|
| Biostatistics | N/A | | | |
| Pharmacology/Toxicology | N/A | | | |
| CDRH-ODE | N/A | | | |
| CDRH-OC | N/A | | | |
| Clinical | N/A | | | |
| Other | N/A | | | |

*Application Technical Lead Name and Date:*

*Renishkumar Delvadia, 09/13/2021*

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/s/

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RENISHKUMAR R DELVADIA
09/14/2021 11:21:41 AM

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

# RECOMMENDATION

| |
|---|
| ☐ Approval |
| ☐ Approval with Post-Marketing Commitment |
| ☒ Complete Response |

# NDA 213426
# Assessment # 1

| | |
|---|---|
| **Drug Product Name** | Celecoxib and Tramadol hydrochloride, Tablets |
| **Dosage Form** | Tablet |
| **Strength** | 56 mg celecoxib and 44 mg tramadol HCl |
| **Route of Administration** | oral |
| **Rx/OTC Dispensed** | Rx |
| **Applicant** | Esteve Pharmaceuticals, S.A. |
| **US agent, if applicable** | Rebecca Nortz, c/o Esteve Pharmaceuticals, LLC |

| Submission(s) Assessed | Document Date | Discipline(s) Affected |
|---|---|---|
| 0001 (1) Original submission | 05/15/2019 | All |
| 0004 (4) Quality/IR response | 06/18/2019 | Drug Substance, OPMA |
| 0005 (5) Quality/IR response | 07/01/2019 | OPMA |
| 0007 (7) Multiple categories/IR responses | 08/02/2019 | Drug product, OPMA, Biopharm. |
| 0010 (10) Multiple categories/IR responses | 09/27/2019 | Drug Substance, Drug product |
| 0014 (14) Multiple categories/IR responses | 10/31/2019 | OPMA, Drug Substance |
| 0016 (16) Multiple categories/IR responses | 11/19/2019 | OPMA |
| 0018 (18) Labeling/container-carton draft | 12/10/2019 | Drug product |
| 0019 (19) Quality/IR responses | 12/16/2019 | OPMA |

| | | |
|---|---|---|
| 0021 (21) Quality/IR responses | 12/20/2019 | OPMA |
| 0025 (25) Multiple/IR responses | 03/11/2020 | OPMA |
| 0026 (26) Quality/IR responses | 03/30/2020 | Drug product |

**QUALITY ASSESSMENT TEAM**

| Discipline | Primary Assessment | Secondary Assessment |
|---|---|---|
| **Drug Substance** | Sukhamaya Bian | Donna Christner |
| **Drug Product** | Renishkumar Delvadia | Julia Pinto |
| **Manufacturing** | Tarun Mehta | Ubrani Venkataram<br><br>Jonathan Swoboda |
| **Microbiology** | N/A | N/A |
| **Biopharmaceutics** | Kalpana Paudel | Hansong Chen |
| **Regulatory Business Process Manager** | Anika Lalmansingh | |
| **Application Technical Lead** | Renishkumar Delvadia | |
| **Laboratory (OTR)** | N/A | |
| **Environmental** | N/A | |

# EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

*This application is NOT recommended for approval by OPMA. Facility reviewer, Dr. Tarun Mehta, noted in his review that the field investigator could not complete inspection of the* (b) (4) *manufacturing facility* (b) (4) *because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. The Application is approvable from drug substance, biopharmaceutics, manufacturing process, labeling, and drug product perspective.*

## II. SUMMARY OF QUALITY ASSESSMENTS

## A. Product Overview

The proposed drug product is a white to off-white, elongated coated tablet, debossed with "100" on one side and "CTC" on the other side. The tablets contain 100 mg of co-crystal containing 56 mg of celecoxib and 44 mg of tramadol hydrochloride. The coated tablets will be packaged in white, opaque high-density polyethylene (HDPE) bottles with (b) (4) child resistant screw-cap and tamper evidence (b) (4) (b) (4) The 30-count configuration will be filled in 35-mL bottles and the 90-count configuration will be filled in 50-mL bottle

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | For the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. |
| **Duration of Treatment** | |
| **Maximum Daily Dose** | The Maximum daily dose is 400 mg of co-crystal equivalent to 224 mg of Celecoxib and 176 mg of Tramadol HCl. |
| **Alternative Methods of Administration** | N/A |

## B. Quality Assessment Overview

**Drug Substance:** Adequate

The drug substance, co-crystal of celecoxib and tramadol HCl, is recommended for approval from the perspective of the drug substance reviewer. The applicant has referenced DMF (b) (4) which has referenced secondary DMFs (b) (4) All three DMFs have been found adequate by the Agency. The co-crystal specification is consistent with the USP monographs of the respective API components and ICH Q6A guidelines. The specified individual impurity limits are within ICH Q3A guidelines. The DMF (b) (4) is adequate with a retest period of (b) (4) months for the co-crystal, when stored at (b) (4) ºC.

**Drug Product: Adequate**

The tablets contain 100 mg of co-crystal containing 44 mg of tramadol hydrochloride and 56 mg of celecoxib. The proposed to-be-marketed (TBM) formulation compositions of proposed drug product contains excipients (b) (4)

(b) (4) The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the drug substance. The proposed formulation is (b) (4) The coated tablets will be packaged in white, opaque high-density polyethylene (HDPE) bottles with (b) (4) child resistant screw-cap and tamper evidence (b) (4) The 30-count configuration will be filled in 35-mL bottles and the 90-count configuration will be filled in 50-mL bottle. The overall stability data provided by the Applicant, support the proposed shelf-life of 24 months. Applicant has demonstrated (b) (4) No CMC approvability issue is found related to the proposed drug product.

**Labeling: Adequate**

**Manufacturing: Adequate**

The DP manufacturing process consist of (b) (4) The proposed critical in-process controls (IPCs) include (b) (4) The Application is adequate from process perspective. The field investigator could not complete inspection of the (b) (4) manufacturing facility (b) (4) (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved.

| Facility name and address | FEI | Responsibilities and profile code(s) | Status |
|---|---|---|---|
| (b) (4) | | Manufacturing, quality control testing, stability testing, packaging, batch release and storage of the drug substance. \|\| DMF: (b) (4) \|\| 356h (b) (4) | Approve - Based on Previous History |
| | | Testing (b) (4) for the batch release of the drug substance. \|\| DMF (b) (4) \|\| 356h Status: LCP | Approve - Based on Previous History |

| | | | |
|---|---|---|---|
| (b) (4) | | Manufacturing and testing of Celecoxib (b) (4) \|\| DMF: (b) (4) \|\| 356h Status: (b) (4) | Approve - Based on Previous History |
| | | Manufacturing and testing of Tramadol HCl \|\| DMF: (b) (4) \|\| 356h Status: (b) (4) | Approve - Based on Previous History |
| | | Manufacturing and testing (b) (4) (b) (4) \|\| 356h Status: (b) (4) | Approve - Based on Previous History |
| | | Manufacturing and testing (b) (4) (b) (4) \|\| 356h Status: (b) (4) | Withhold - Not Ready |
| | | Manufacturing and testing (b) (4) (b) (4) \|\| 356h Status: (b) (4) | Withdrawn |
| | | Celecoxib (b) (4) release testing \|\| 356h Status: PendingCelecoxib (b) (4) release testing \|\| 356h Status: Pending<br><br>LCP | Approve - Based on Previous History |
| Esteve Pharmaceuticals, S.A.Esteve Pharmaceuticals, S.A.<br><br>C/ de Sant Martí, 75-97 , Martorelles, Barcelona, Spain, | 3003121577 | Drug product manufacturer for Celecoxib and Tramadol, Tablets. Responsible for manufacturing, packaging, labeling, release testing (drug product and components) and stability testing. \|\| 356h Status: | Approve - Based on Previous History |

| | | | |
|---|---|---|---|
| 8107C/ de Sant Martí, 75-97 , Martorelles, Barcelona, Spain, 8107 | | TCM | |
| (b) (4) | | (b) (4) Testing of Celecoxib-Tramadol, co-crystal API (drug substance). \|\| 356h Status: Pending (b) (4) Testing of Celecoxib-Tramadol, co-crystal API (drug substance). \|\| 356h Status: Pending<br><br>LCP | Approve - Based on Previous History |
| | | Testing of USP/NF excipients used in drug product manufacture of Celecoxib and Tramadol, Tablets \|\| 356h Status: PendingTesting of USP/NF excipients used in drug product manufacture of Celecoxib and Tramadol, Tablets \|\| 356h Status: Pending<br><br>LCP | No Evaluation Necessary |

**Biopharmaceutics: Adequate**

The biopharmaceutics review focused on the evaluation of the dissolution method and acceptance criterion for (b) (4) (tramadol and celecoxib) tablet and the bridging between the to-be-marked formulation and pivotal clinical formulations. Phase 3 clinical study (ESTEVE-SUSA-301 in USA) (b) (4) is the same as the to-be-marketed formulation. The dissolution profiles of tramadol HCl and celecoxib from exhibit stability batches were similar to the dissolution profiles of this Phase 3 clinical batch. In response to an IR, the Applicant accepted the Agency recommended Q= (b) (4) % in 15 minutes for both tramadol and celecoxib. Note that the Applicant has conducted some clinical trials using (b) (4) tablets (b) (4) The Applicant has provided comparative dissolution profiles between (b) (4) (b) (4) tablets to establish the bridging.

## C. Risk Assessment

| From Initial Risk Identification | | | Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking** | **Risk Mitigation Approach** | **Final Risk Evaluation** | **Lifecycle Considerations/ Comments** |
| Assay, Stability | Formulation<br>• Container closure<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | (b) (4) | Acceptable | None |

| | | | (b) (4) | | |
|---|---|---|---|---|---|
| Physical stability (solid state) | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site<br>• | M | | Acceptable | None |
| Content uniformity | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | | Acceptable | None |
| Microbial limits | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | L | | Acceptable | None |
| Dissolution | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | | Acceptable | None |

## D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

Major deficiency (approvability issue), that must be addressed prior to a subsequent NDA resubmission:

**Deficiency:** Our field investigator could not complete inspection of the [redacted] (b) (4) manufacturing facility [redacted] (b) (4) because the facility was not ready for inspection.

**Information to resolve deficiency**: Satisfactory inspection is required before this NDA may be approved. Please notify us in writing when this facility is ready for inspection.

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

# QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Assessment Completed | Comments |
|---|---|---|---|---|---|---|
| [redacted] (b) (4) | II | [redacted] | [redacted] (b) (4) | Active | 10/11/2019 | |
| | II | | | Active | 08/19/2019 | |
| | II | | | Active | 08/27/2019 | |
| | III | | | Active | N/A | Sufficient information in application |
| | IV | | | Active | N/A | Sufficient information in application |

| | | | (b) (4) | | | |
|---|---|---|---|---|---|---|

**B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA***

| Document | Application Number | Description |
|---|---|---|
| NDA | 02028 | Ultram, Janseem Pharms |
| NDA | 021692 | Ultram ER, Valeant Pharms |
| NDA | 020998 | Celebrex, GD Searle |
| IND | 128177 | Co-crystal E-58425, LABORATORIOS DEL DR ESTEVE SA |

**2. CONSULTS**

| Discipline | Status | Recommendation | Date | Assessor |
|---|---|---|---|---|
| Biostatistics | N/A | | | |
| Pharmacology/Toxicology | N/A | | | |
| CDRH-ODE | N/A | | | |
| CDRH-OC | N/A | | | |
| Clinical | N/A | | | |
| Other | N/A | | | |

*Application Technical Lead Name and Date:*

*Renishkumar Delvadia, 05/12/2020*



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# CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

## 1.0 PRESCRIBING INFORMATION

**Assessment of Product Quality Related Aspects of the Prescribing Information:**

### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Product Title in Highlights** | | |
| Proprietary name | (b) (4) | |
| Established name(s) | (celecoxib and tramadol hydrochloride) Tablets | Acceptable |
| Route(s) of administration | **oral use** | Acceptable |
| **Dosage Forms and Strengths Heading in Highlights** | | |
| Summary of the dosage form(s) and strength(s) in metric system. | Tablets: (b) (4) (b) (4) | Not acceptable: (b) (4) "celecoxib 56 mg and tramadol hydrochloride 44 mg" |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | N/A | |

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE AND ADMINISTRATION section** | | |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product) | (b) (4) | Not acceptable; (b) (4) (b) (4) (b) (4) The statement should be edited to "The dose of (b) (4) 56 mg/44 mg is 2 tablets every 12 hours." |

**Section 3 (DOSAGE FORMS AND STRENGTHS)**

APPEARS THIS WAY ON ORIGINAL

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE FORMS AND STRENGTHS section** | | |
| Available dosage form(s) | coated tablets | Acceptable |
| Strength(s) in metric system | (b) (4) | Not acceptable: the statement should be "(b) (4) coated tablets contain 56 mg celecoxib and 44 mg tramadol hydrochloride" |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance | Celecoxib strength is based on celecoxib amount in co-crystal.<br><br>Tramadol hydrochloride strength is based on amount of salt in co-crystal; | Acceptable; USP exemption is applied since the previous tramadol product strengths are based on tramadol hydrochloride. |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting | The tablets are white to off-white elongated coated tablets debossed with "100" on one side and "CTC" on the other. | Acceptable; debossing "100" and "CTC" were found acceptable by DMEPA. |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | N/A |

| | | |
|---|---|---|
| For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package. | N/A | |

APPEARS THIS WAY ON ORIGINAL

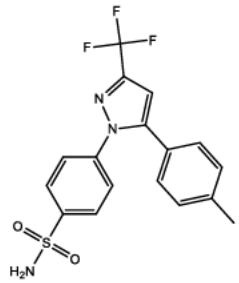
### 1.2.2 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DESCRIPTION section** | | |
| Proprietary and established name(s) | (b) (4) | Acceptable; |
| Dosage form(s) and route(s) of administration | ((celecoxib and tramadol) Tablets | Acceptable. |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. | (b) (4) | Not acceptable: Equivalence statement needed for tramadol base; "(b) (4) coated tablets contain 56 mg celecoxib and 44 mg of tramadol hydrochloride (equivalent to XX mg of tramadol base) in a co-crystal structure." |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. | Inactive ingredients in the tablet are sodium lauryl sulfate, crospovidone, mannitol, sodium stearyl fumarate, talc, cellulose microcrystalline, copovidone and color mixture (polyvinyl alcohol partially hydrolized, titanium dioxide, polyethylene glycol and talc). | Acceptable. |
| For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. | N/A | N/A |

| | | |
|---|---|---|
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | N/A |
| Statement of being sterile (if applicable) | N/A | N/A |
| Pharmacological/ therapeutic class | an analgesic and opioid agonist and inhibitor (b) (4) (b) (4) | No acceptable; should be changed according to DAAP recommendation. |

APPEARS THIS WAY ON ORIGINAL

| | | |
|---|---|---|
| Chemical name, structural formula, molecular weight | Tramadol HCl:<br>The chemical name for tramadol hydrochloride is (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride<br>(b) (4) | Tramadol: Not acceptable; Should be replaced with a (b) (4) structure.<br><br>Clarification needed (b) (4)<br><br>Celecoxib: Acceptable.<br><br>Co-crystal: Applicant will be asked to include information on molar ratios of individual components in a co-crystal structure. |
| | The molecular weight of tramadol hydrochloride is 299.84.<br><br>Celecoxib:<br>The chemical name for celecoxib is 4-[5-(4-methylphenyl)- 3-(trifluoromethyl)-1*H*-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The molecular weight is 381.38 and it has the following chemical structure:<br>  | |
| If radioactive, statement of important nuclear characteristics. | N/A | N/A |

| | | |
|---|---|---|
| Other important chemical or physical properties (such as pKa or pH) | N/A | N/A |

**Section 11 (DESCRIPTION) Continued**

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| For oral prescription drug products, include gluten statement if applicable | Not provided | |
| Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity" | None | The Applicant will be asked to limit mentioning about co-crystal to Section 11. |

### 1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Available dosage form(s) | coated tablets | Acceptable |
| Strength(s) in metric system | (b) (4) | Not acceptable; statement should be "(b) (4) ((celecoxib and tramadol hydrochloride) Tablets) coated tablets contain 56 mg celecoxib and 44 mg tramadol hydrochloride." |
| Available units (e.g., bottles of 100 tablets) | (b) (4) | Not acceptable: correct NDC codes should in included Bottles of 30 tablets: NDC 68118-258-64 Bottles of 90 tablets: NDC 68118-258-70. |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | The tablets are to off-white elongated coated tablets debossed with "100 on one side and "CTC" on the other side | Acceptable |

| | | |
|---|---|---|
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | N/A |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | N/A | N/A |

**Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)**

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|

| | | |
|---|---|---|
| Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.) | Dispense in a tight container. | Acceptable |
| If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.” | N/A | Acceptable. |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. | Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). [see USP Controlled Room Temperature]. | Acceptable. |
| Include information about child-resistant packaging | Does not claim “child-resistant closure” | Acceptable |

### 1.2.4 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

(b) (4)

DAAAP has been notified regarding this during the first labelling review meeting.

### *1.2.5* Manufacturing Information After Section 17 (for drug products)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Manufacturing Information After Section 17** | | |
| Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer | (b) (4) | Acceptable. |

## 2.0 PATIENT LABELING

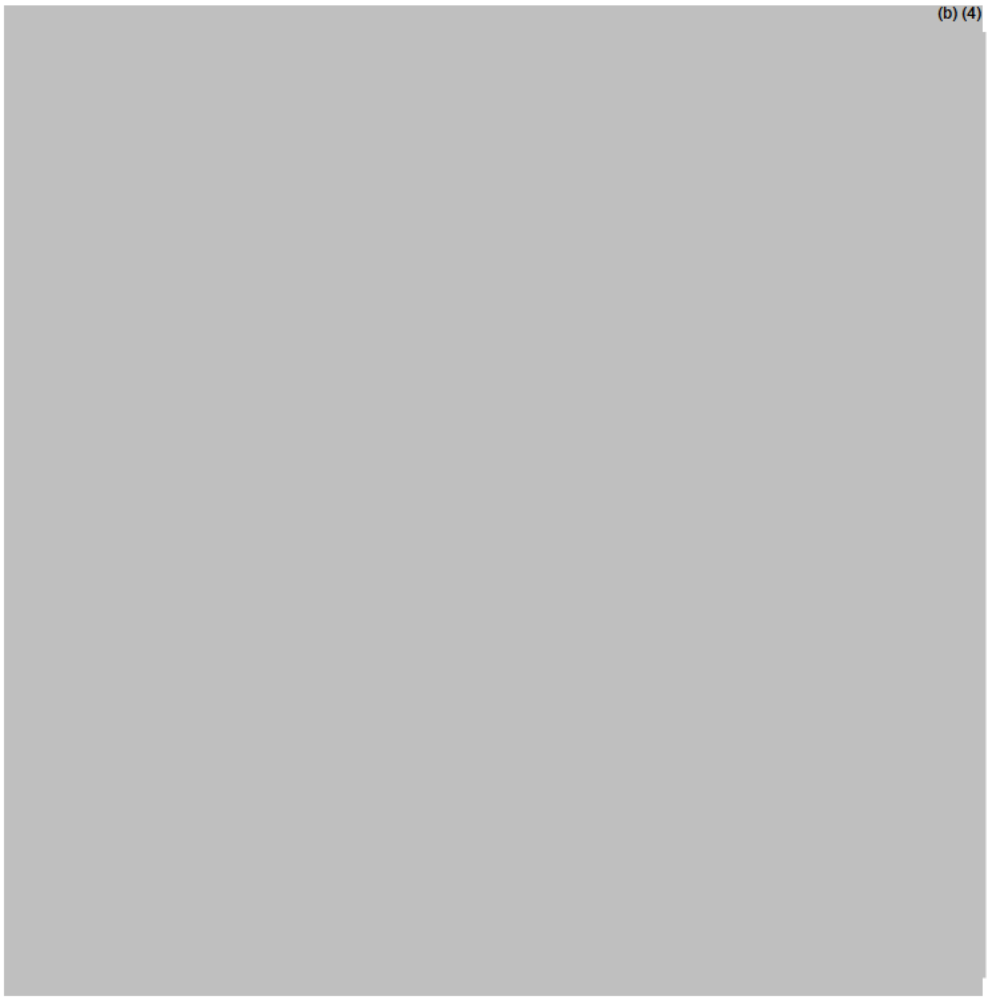
**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):**

None

**Acceptable.**

## 3.0 CARTON AND CONTAINER LABELING

**3.1 Carton Label**
**30 counts**




**90 counts**


### 3.2 Container Labeling

*(Copy/paste or refer to a representative example of a proposed carton labeling)*

*30 tablets:*


*90 tablets:*



1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

| Item | Information Provided in the NDA | Assessor's Comments about Container Labeling |
|---|---|---|
| Proprietary name, established name, and dosage form (font size and prominence | Tradename not included | Not acceptable |
| Dosage strength | 56 mg/44 mg | Acceptable |
| Route of administration | Not included | |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance | No Tramadol hydrochloride equivalency statement | Not acceptable; Equivalency statement needed for tramadol HCl. |
| Net contents (e.g. tablet count) | 30 or 90 counts | Acceptable |
| "Rx only" displayed on the principal display | Displayed | Acceptable |
| NDC number | Displayed | Acceptable |
| Lot number and expiration date | Displayed | Acceptable |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD. | Displayed | Acceptable |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use) | N/A | N/A |
| Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement. | N/A | N/A |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | N/A |
| Bar code | Displayed | Acceptable |

| Item | Information Provided in the NDA | Assessor's Comments about Carton Labeling |
|---|---|---|
| Name of manufacturer/distributor | Displayed | Acceptable |
| Medication Guide (if applicable) | Instruction to read the prescribing information. | Acceptable |
| No text on Ferrule and Cap overseal | N/A | N/A |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. | N/A | N/A |
| And others, if space is available | N/A | N/A |

**Assessment of Carton and Container Labeling: *Adequate***

## ITEMS FOR ADDITIONAL ASSESSMENT

***Overall Assessment and Recommendation:***

**Adequate with the following deficiency.**

**Include an equivalency statement for tramadol HCl indicating the strength in terms of the active moiety, tramadol. The equivalency statement should appear on the container label, carton labeling, and other labeling.**

*Primary Labeling Assessor Name and Date: Renishkumar Delvadia, 01/19/2020*

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

Renishkumar Delvadia

Digitally signed by Renishkumar Delvadia
Date: 1/23/2020 12:38:13PM
GUID: 5388ee7d000671ff7781f1835a3ff7b9

Julia Pinto

Digitally signed by Julia Pinto
Date: 1/23/2020 01:15:47PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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# BIOPHARMACEUTICS

**Product Background:**

**NDA:** NDA-213426-ORIG-1

**Drug Product Name / Strength:** (b) (4) (tramadol and celecoxib) Tablet/100 mg (44 mg tramadol and 56 mg celecoxib)

**Route of Administration:** Oral

**Applicant Name:** ESTEVE PHARMACEUTICALS, S.A.

**Submission:**
Esteve Pharmaceuticals has submitted this NDA for (b) (4) (tramadol and celecoxib) Tablet/100 mg (44 mg tramadol and 56 mg celecoxib) for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Co-crystal of Tramadol and Celecoxib is a new Co-Crystal E-58425 composed by rac-Tramadol HCl / Celecoxib 44:56 (w/w).

The final dosing schedule in adults for Celecoxib and Tramadol Tablets is 200 mg every 12 hours as needed.

***Review Recommendation:*** **ADEQUATE**

***Review Summary:***
The biopharmaceutics review is focused on the evaluation of the dissolution method and acceptance criterion for (b) (4) (tramadol and celecoxib) tablet and the bridging between the to-be-marked formulation and pivotal clinical formulations.

**Dissolution Method and Acceptance Criterion: ADEQUATE**
The following dissolution method and acceptance criterion for the release of tramadol and celecoxib from the (b) (4) Tablet are approved:

| USP Apparatus | Speed (RPMs) | Medium/Temperature | Volume (mL) | Acceptance criterion |
|---|---|---|---|---|
| II (Paddle) | 75 | 0.1N HCl + 2% SLS | 1000 mL | Q = (b) (4) % in 15 minutes for both tramadol and celecoxib |

**Bridging of clinical formulations: ADEQUATE**
Phase 3 clinical study (ESTEVE-SUSA-301 in USA) was performed with the Co-crystal E-58425 100 mg coated tablet formulation ( (b) (4) batch #862110) which is same as the to-be-marketed formulation. The dissolution profiles of Tramadol HCl and Celecoxib from exhibit batches are similar to the dissolution profiles of the clinical batch.

**Biowaiver Request: Not requested**
Only one strength is developed.

**List of Submissions reviewed:**

| |
|---|
| Application 213426 - Sequence 0001 - 0001 (1) 05/15/2019 ORIG-1 /Multiple Categories/Subcategories |
| Application 213426 - Sequence 0007 - 0007 (7) 08/02/2019 ORIG-1 /Multiple Categories/Subcategories |

**Highlight Key Outstanding Issues from Last Cycle:** The Applicant was requested to submit the complete Tramadol HCl and Celecoxib dissolution data for the dissolution method development studies, for clinical batch 862110, and was requested to revise the dissolution acceptance criterion.

**Concise Description of Outstanding Issues Remaining:** None.

**Conclusion**
From biopharmaceutics perspective, NDA 213426 for (b) (4) (tramadol and celecoxib/44 mg tramadol and 56 mg celecoxib) is recommended for APPROVAL.

## BCS Designation

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

Pharmaceutical Development report suggests that Tramadol HCl belongs to BCS I and Celecoxib to BCS II. However, the Applicant has not claimed or requested any BCS classification for their drug product.

**Solubility**
The solubility of the Co-crystal E-58425 in different pH buffers is provided below.

**Table 1: Solubility of Co-crystal E-58425 in different pH buffers**

| | Co-crystal E-58425 Room temperature | |
|---|---|---|
| | **TRAMADOL** | **CELECOXIB** |
| 0.1N HCl | > 9 mg/mL | 0.0006 mg/mL |
| pH 4.5 | > 9 mg/mL | 0.0006 mg/mL |
| pH 6.8 | > 9 mg/mL | 0.001 mg/mL |
| pH 12 | 0.37 mg/mL | 0.29 mg/mL |
| (b) (4) | | |

Celecoxib is only soluble at pH 12, but at this pH the solubility of Tramadol is much lower (pka Tramadol HCl = 9.6) (b) (4)

**Table 2: Solubilities of Tramadol and Celecoxib in different media**

| | Co-Crystal of Tramadol and Celecoxib Room temperature | |
|---|---|---|
| | **TRAMADOL** | **CELECOXIB** |
| 0.1N HCl | > 9 mg/mL | 0.0006 mg/mL |
| (b) (4) | | |

**Dissolution:** Please see below.

## Drug Product

(b) (4) (Celecoxib and Tramadol, Tablets) is an immediate-release (b) (4) coated tablet for oral administration containing as drug substance a co-crystal of rac-tramadol HCI (racemic tramadol hydrochloride, also referred to as the cis-diastereoisomer of tramadol or +/- tramadol) and celecoxib. A 100 mg tablet of Celecoxib and Tramadol contains 44 mg of rac-tramadol HCI and 56 mg of celecoxib as the active pharmaceutical ingredients. The proposed indication is the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

The product and process development were conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy. Dissolution was identified as one of the Critical Quality Attributes (CQAs) for the drug product.

The composition of the drug product is provided below.

**Table 3: Composition of (b) (4) Tablet**

| Name of the ingredients | Unit Composition % (w/w) | Unit Composition (mg) | Function | Amount per maximum Daily Dose (mg) | IIG Levels[1] (Oral tablet) (mg) | Quality standards |
|---|---|---|---|---|---|---|
| **Drug substance** | | | | | | |
| Celecoxib-Tramadol, co-crystal[2] | (b) (4) | 100.00 | Drug substance | 400.00 | -- | In-house |
| **Excipients** | | | | | | (b) (4) |
| Sodium lauryl sulfate | (b) (4 | | | | | |
| Crospovidone | (b) (4 | | | | | |
| Mannitol | (b) (4 | | | | | |
| Sodium stearyl fumarate | (b) (4 | | | | | |
| Talc | (b) (4 | | | | | |
| Microcrystalline Cellulose | (b) (4 | | | | | |
| Copovidone | (b) (4 | | | | | |
| Color mixture[4][5] | (b) (4 | | | | | |
| *Total* (b) (4) *coated tablet (mg)* | | | | | | (b) (4) |

## Dissolution Method and Acceptance Criterion

**Reviewer's Assessment: Adequate**

The biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criterion for the release of tramadol and celecoxib from the (b) (4) Tablet.

### Proposed dissolution method and acceptance criterion

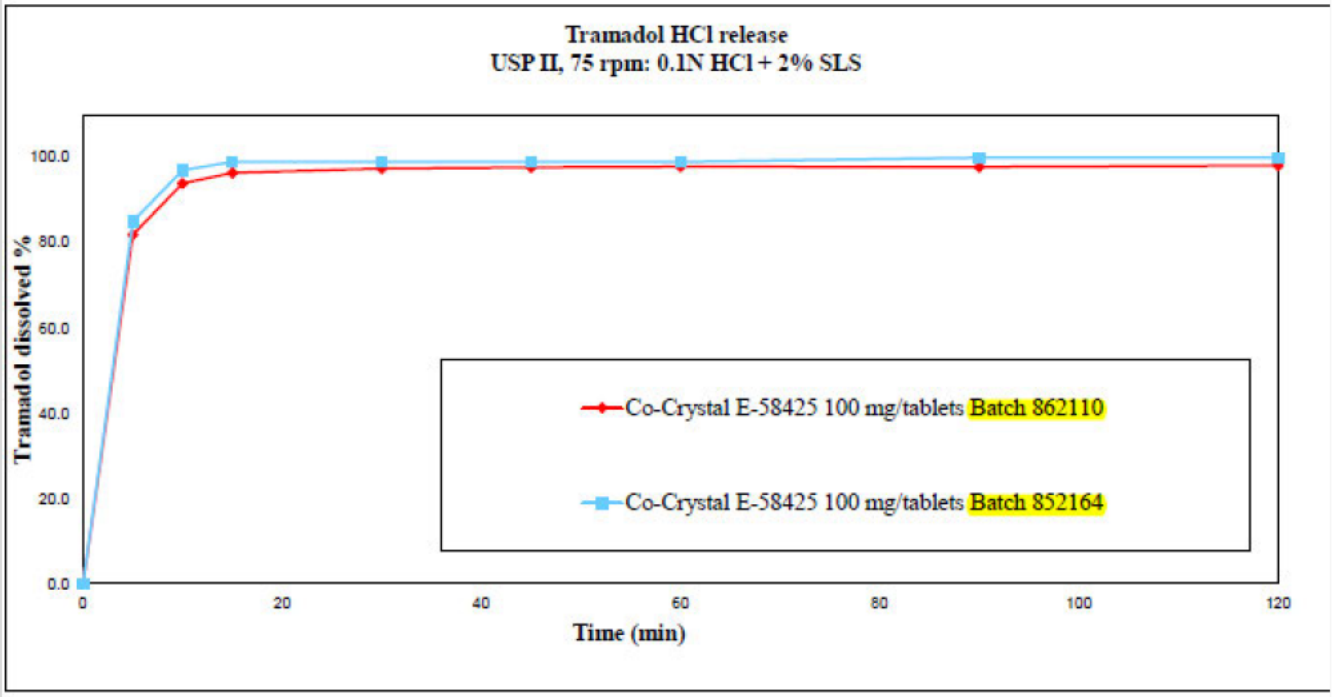
The following dissolution method and acceptance criterion were proposed:

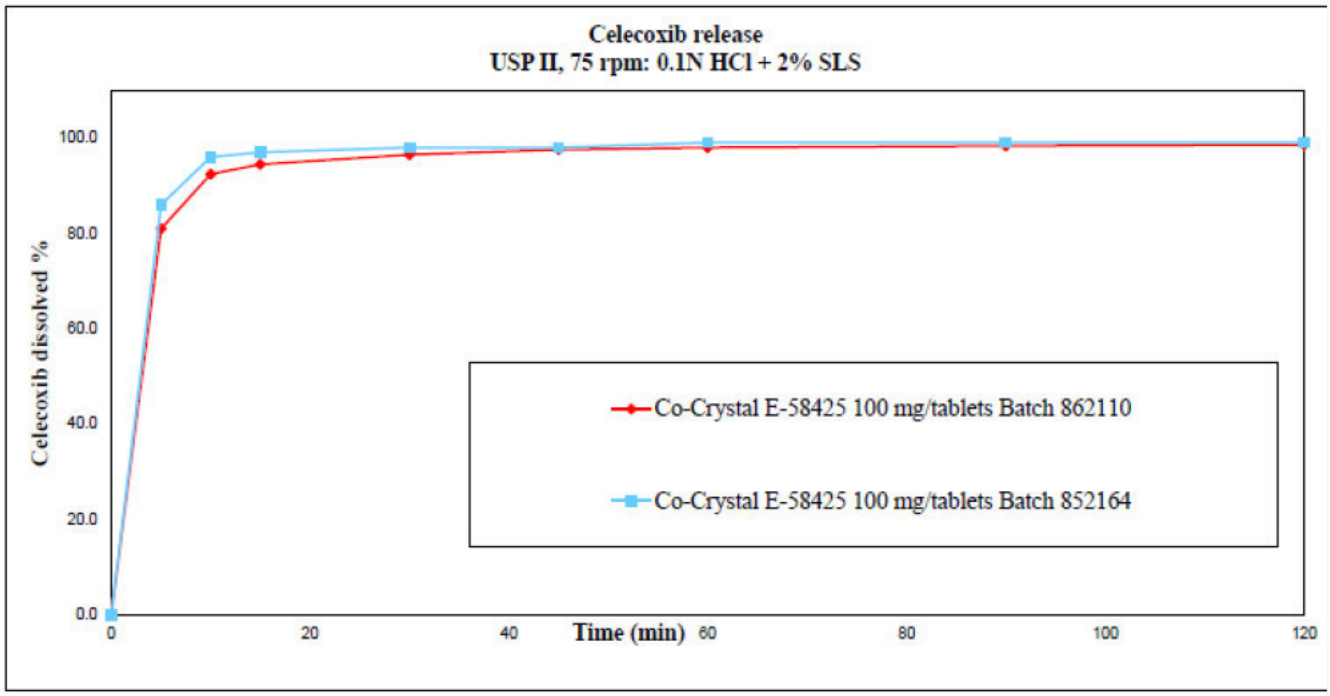
**Table 4: Dissolution Method for (b) (4) Tablet**

| USP Apparatus | Speed (RPMs) | Medium/Temperature | Volume (mL) | Acceptance criterion |
|---|---|---|---|---|
| II (Paddle) | 75 | 0.1N HCl + 2% SLS | 1000 mL | Q = (b) (4)% in (b) (4) minutes for both APIs |

In response to an IR (please see Appendix 1, IR1.2), the Applicant submitted complete dissolution profiles of Tramadol HCl and Celecoxib for Phase 3 clinical batch #862110 as shown below. Dissolution profiles of another batch (Batch #852164) was similar to the clinical batch showing batch-to-batch consistency. The dissolution data for 3 exhibit batches are also provided in Module 3.2.P.8.3 Stability Data; \\cdsesub1\evsprod\nda213426\0007\m3\32-body-data\32p-drug-prod\celecoxibtramadol-tablets\32p8-stab\stability-data.pdf).

. **Figure 1: Dissolution profile of (b) (4) Tablet Batch #862110**




The Applicant's proposed dissolution acceptance criterion is Q= (b)(4)% in (b)(4)minutes for both APIs. In response to an IR (IR1.3), the Applicant accepted the Agency recommended Q= (b)(4)% in 15 minutes for both tramadol and celecoxib. The dissolution data for 3 exhibit batches comply with this tightened acceptance criterion.

**Dissolution method development**

(b) (4)

The details of the dissolution method development for the co-crystal tablet is provided in Module 3.2.P.2.4 Pharmaceutical Development (\\cdsesub1\evsprod\nda213426\0010\m3\32-body-data\32p-drug-prod\celecoxibtramadol-tablets\32p2-pharm-dev\pharmaceutical-development.pdf). In response to an IR (IR1.1), the Applicant provided complete dissolution data for the profiles in dissolution method development studies. Module 3.2.P.5.6 Justification of Specifications further justifies the dissolution method.

**Discriminating ability of the dissolution method**

The details of the discriminating ability of the proposed dissolution method is provided in Module 3.2.P.2.4 Pharmaceutical Development (\\cdsesub1\evsprod\nda213426\0010\m3\32-body-data\32p-drug prod\celecoxibtramadol-tablets\32p2-pharm-dev\pharmaceutical-development.pdf). In summary, batches containing drug substances with different PSD, ranging d(90) from (b) (4) µm were used to evaluate the discriminatory power of the proposed dissolution method.

**Figure 2: Tramadol HCl dissolution profiles for Co-crystal E-58425 (b) (4) mg tablets manufactured with drug substances with different PSD**

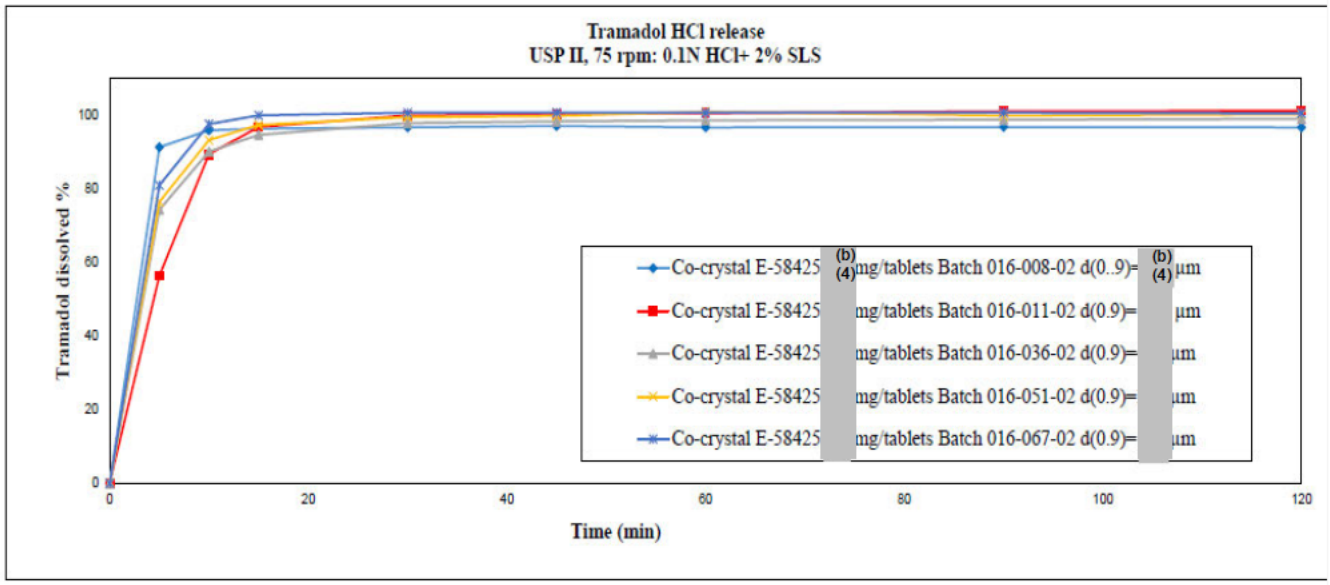
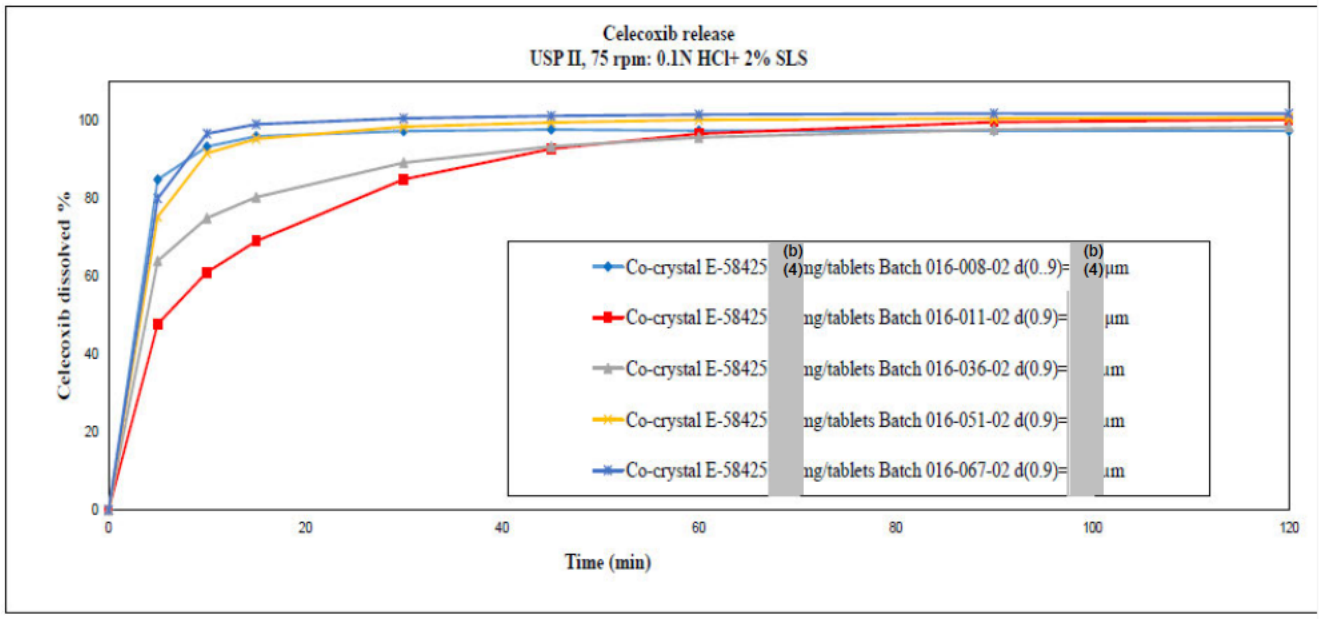



**Figure 2: Celecoxib dissolution profiles for Co-crystal E-58425 (b) (4) mg tablets manufactured with drug substances with different PSD.**




As can be seen in the figures above, different dissolution profiles were obtained for drug product containing drug substances Co-crystal E-58425 with different PSD showing that dissolution method has some discriminating ability. However, for tramadol, all dissolution profiles (n=6) met the proposed acceptance criterion. For celecoxib, co-crystals with particle sizes (b) (4) µm did not meet the acceptance criterion, showing that the proposed acceptance criterion is also sensitive to the particle size variation.

**Reviewer's assessment:**

- The Applicant has developed and validated a dissolution method using USP apparatus II. The dissolution method development report has been submitted. The proposed dissolution method has some discriminating ability towards particle size variation of the co-crystal. The proposed dissolution method is acceptable.
- The Applicant's proposed dissolution acceptance criterion is Q= (b) (4)% in (b) (4) minutes for both APIs. In response to an IR, the Applicant accepted the Agency recommended Q= (b) (4)% in 15 minutes for both tramadol and celecoxib.

## Bridging of Formulations

**Reviewer's Assessment: Adequate**

The Applicant initially conducted clinical trials using (b) (4) formulation as shown below.

| Clinical trials | Formula evaluated | Drug product batch number | Strength and details |
|---|---|---|---|
| ESTEVE-SACO4-103 (TAI-PO-692) | (b) (4) | 802659 (b) (4)<br>802660 (b) (4) | (b) (4) |
| ESTEVE-SACO4-102 (TAI-P0-584) | | 802660 | |
| ESTEVE-SACO4-104 (TAI-P1-585) | | 812513 | |
| ESTEVE-SACO4-105 | | 812513 | |
| ESTEVE-SACO4-201 | | 812516<br>812517<br>812518 | |

However, Phase 1 clinical study ESTEVE-SUSA-101 and Phase 3 ESTEVE-SUSA-301 in USA were performed with the Co-crystal E-58425 100 mg (b) (4) tablets formulations (b) (4) (b) (4) which is same as the to-be-marketed formulation (composition shown in table 3). The clinical batch #862110 was used in both clinical studies as shown below. The dissolution profiles of Tramadol HCl and Celecoxib from this clinical batch is presented in Figure 1. The dissolution profiles of exhibit batches are similar to this batch, both meeting the dissolution acceptance criterion.

The Applicant has provided comparative dissolution profiles between (b) (4) (b) (4) tablets as shown below which shows similar dissolution profiles.

**Figure 3: Dissolution profile comparison of Tramadol in Co-crystal E-58425 100 mg (b) (4) (b) (4) tablets 0.1N HCl + 2% SLS**

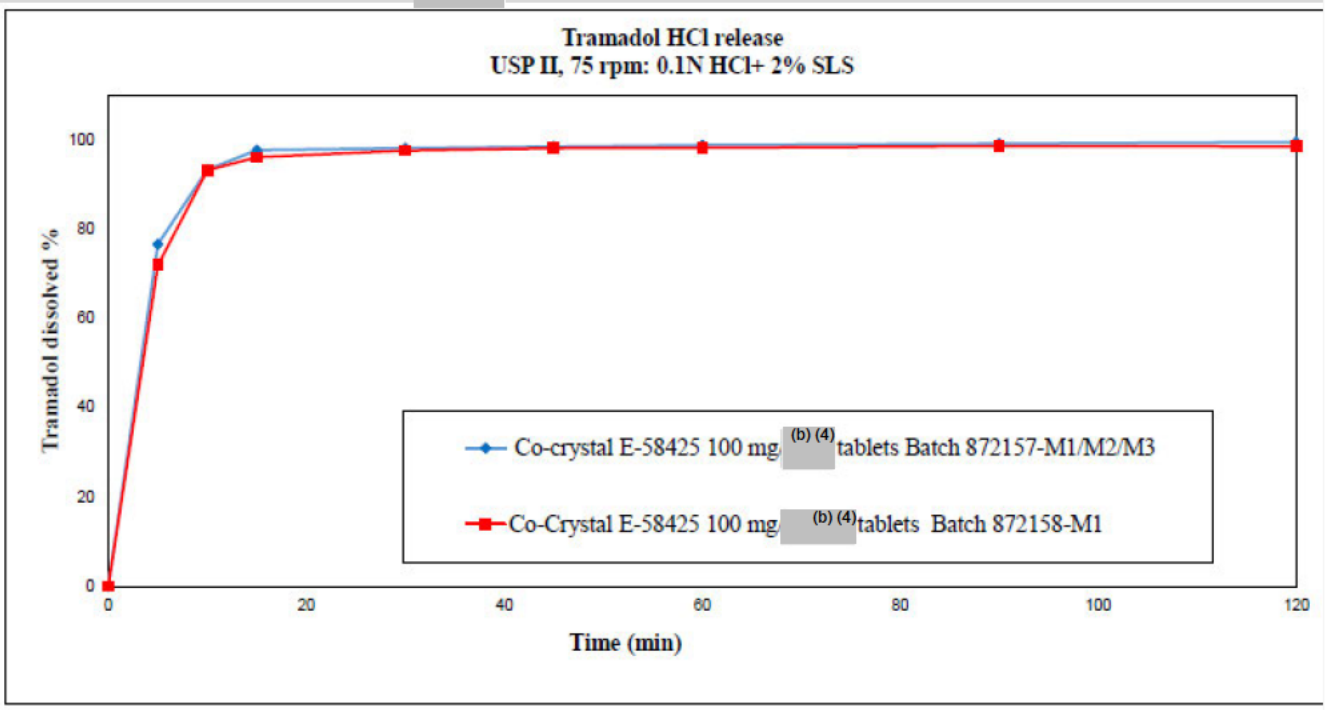
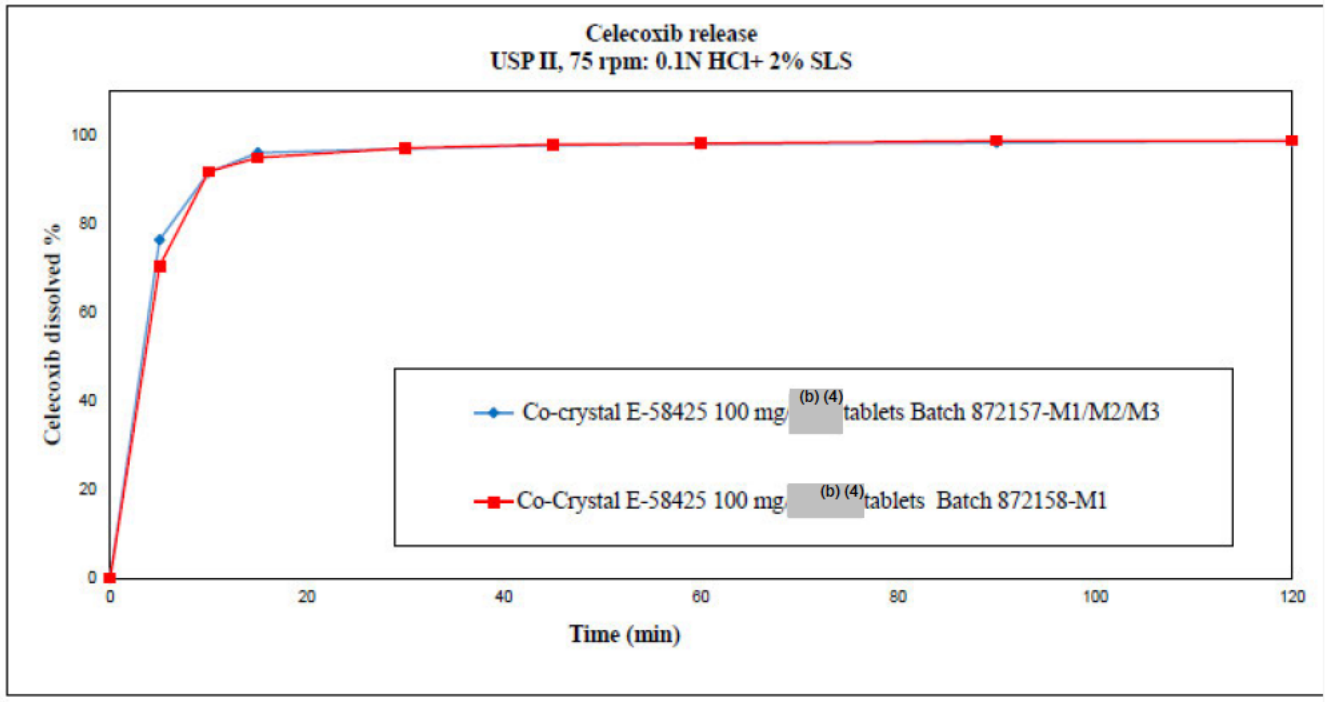



**Figure 4: Dissolution profile comparison of Celecoxib in Co-crystal E-58425 100 mg (b) (4) (b) (4) tablets 0.1N HCl + 2% SLS**



**Biowaiver Request**

**Reviewer's Assessment:** The Applicant has not requested any biowaiver. There is only one strength of the drug product.

**Conclusions and recommendation**

From Biopharmaceutics perspective, NDA 213426 is recommended for APPROVAL.

# *Appendix 1*

***The Information Request conveyed to the Applicant during the review process***

**Information Request 1 (IR 1)**

(b) (4)

[redacted]

***Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.***

***Secondary Reviewer Name: Hansong Chen, PharmD, Ph.D.***

Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 1/17/2020 03:17:05PM
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Hansong Chen

Digitally signed by Hansong Chen
Date: 1/17/2020 03:26:29PM
GUID: 525d7d660003845a197a2e1682433d0d

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

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/s/

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RENISHKUMAR R DELVADIA
05/12/2020 03:53:27 PM
This is the revised version of the IQA. Previous version (uploaded on 01/27/2020) lists several minor drug product and manufacturing process related deficiencies that have been resolved since.

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

# RECOMMENDATION

| |
|---|
| ☐ Approval |
| ☐ Approval with Post-Marketing Commitment |
| ☒ Complete Response |

# NDA 213426
# Assessment # 1

| | |
|---|---|
| **Drug Product Name** | Celecoxib and Tramadol hydrochloride, Tablets |
| **Dosage Form** | Tablet |
| **Strength** | 56 mg celecoxib and 44 mg tramadol HCl |
| **Route of Administration** | oral |
| **Rx/OTC Dispensed** | Rx |
| **Applicant** | Esteve Pharmaceuticals, S.A. |
| **US agent, if applicable** | Rebecca Nortz, c/o Esteve Pharmaceuticals, LLC |

| Submission(s) Assessed | Document Date | Discipline(s) Affected |
|---|---|---|
| 0001 (1) Original submission | 05/15/2019 | All |
| 0004 (4) Quality/IR response | 06/18/2019 | Drug Substance, OPMA |
| 0005 (5) Quality/IR response | 07/01/2019 | OPMA |
| 0007 (7) Multiple categories/IR responses | 08/02/2019 | Drug product, OPMA, Biopharm. |
| 0010 (10) Multiple categories/IR responses | 09/27/2019 | Drug Substance, Drug product |
| 0014 (14) Multiple categories/IR responses | 10/31/2019 | OPMA, Drug Substance |
| 0016 (16) Multiple categories/IR responses | 11/19/2019 | OPMA |
| 0018 (18) Labeling/container-carton draft | 12/10/2019 | Drug product |
| 0019 (19) Quality/IR responses | 12/16/2019 | OPMA |
| 0021 (21) Quality/IR responses | 12/20/2019 | OPMA |

**QUALITY ASSESSMENT TEAM**

| Discipline | Primary Assessment | Secondary Assessment |
|---|---|---|
| **Drug Substance** | Sukhamaya Bian | Donna Christner |
| **Drug Product** | Renishkumar Delvadia | Julia Pinto |
| **Manufacturing** | Tarun Mehta | Ubrani Venkataram<br><br>Jonathan Swoboda |
| **Microbiology** | N/A | N/A |
| **Biopharmaceutics** | Kalpana Paudel | Hansong Chen |
| **Regulatory Business Process Manager** | Anika Lalmansingh | |
| **Application Technical Lead** | Renishkumar Delvadia | |
| **Laboratory (OTR)** | Renishkumar Delvadia | Julia Pinto |
| **Environmental** | Sukhamaya Bian | Donna Christner |

# EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

*This application is NOT recommended for approval by OPMA. Facility reviewer, Dr. Tarun Mehta, noted in his review that the field investigator could not complete inspection of the* (b) (4) *manufacturing facility* (b) (4) (b) (4) *because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. There are also additional comments from OPMA and drug product reviewer that are not approvability issues that should be addressed prior to a subsequent NDA resubmission. The Application is approvable from drug substance, biopharmaceutics, and drug product perspective*

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

The proposed drug product is a white to off-white, elongated coated

| |
|---|
| tablet, debossed with “100” on one side and “CTC” on the other side. The tablets contain 100 mg of co-crystal containing 56 mg of celecoxib and 44 mg of tramadol hydrochloride. The coated tablets will be packaged in white, opaque high-density polyethylene (HDPE) bottles with (b) (4) child resistant screw-cap and tamper evidence (b) (4) (b) (4) The 30-count configuration will be filled in 35-mL bottles and the 90-count configuration will be filled in 50-mL bottle |

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | For the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. |
| **Duration of Treatment** | |
| **Maximum Daily Dose** | The Maximum daily dose is 400 mg of co-crystal equivalent to 224 mg of Celecoxib and 176 mg of Tramadol HCl. |
| **Alternative Methods of Administration** | N/A |

## B. Quality Assessment Overview

**Drug Substance:** Adequate

| |
|---|
| The drug substance, co-crystal of celecoxib and tramadol HCl, is recommended for approval from the perspective of the drug substance reviewer. The applicant has referenced DMF (b) (4) which has referenced secondary DMFs (b) (4) All three DMFs have been found adequate by the Agency. The co-crystal specification is consistent with the USP monographs of the respective API components and ICH Q6A guidelines. The specified individual impurity limits are within ICH Q3A guidelines. The DMF (b) (4) is adequate with a retest period of (b) (4) months for the co-crystal, when stored at (b) (4) ºC. |

**Drug Product: Adequate**

| |
|---|
| The tablets contain 100 mg of co-crystal containing 44 mg of tramadol hydrochloride and 56 mg of celecoxib. The proposed to-be-marketed (TBM) formulation compositions of proposed drug product contains excipients (b) (4) The Applicant has performed adequate product development studies to justify the selection of the excipients and to demonstrate/justify their chemical compatibility with the |

drug substance. The proposed formulation is (b) (4) The coated tablets will be packaged in white, opaque high-density polyethylene (HDPE) bottles with (b) (4) child resistant screw-cap and tamper evidence (b) (4) The 30-count configuration will be filled in 35-mL bottles and the 90-count configuration will be filled in 50-mL bottle. The overall stability data provided by the Applicant, support the proposed shelf-life of 24 months. Applicant has demonstrated (b) (4) No CMC approvability issue is found related to the proposed drug product; there are two outstanding deficiencies related to the comparability protocol and drug product labelling listed in the later section below (not approvability issue).

**Labeling: Adequate**

**Manufacturing: Adequate**

The DP manufacturing process consist of (b) (4) The proposed critical in-process controls (IPCs) include (b) (4) he overall process is deemed inadequate due to outstanding deficiencies issues below. Also, the field investigator could not complete inspection of the (b) (4) manufacturing facility (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. The outstanding deficiencies from process and facility perspective are listed in the later section.

| Facility name and address | FEI | Responsibilities and profile code(s) | Status |
|---|---|---|---|
| (b) (4) | | Manufacturing, quality control testing, stability testing, packaging, batch release and storage of the drug substance. \|\| DMF: (b) (4) \|\| 356h (b) (4) | Approve - Based on Previous History |
| | | Testing (b) (4) for the batch release of the drug substance. \|\| DMF: (b) (4) \|\| 356h Status: LCP | Approve - Based on Previous History |
| | | Manufacturing and testing of Celecoxib | Approve - |

| | | | |
|---|---|---|---|
| (b) (4) | | (b) (4) || DMF: (b) (4) || 356h Status: (b) (4) | Based on Previous History |
| | | Manufacturing and testing of Tramadol HCl || DMF: (b) (4) || 356h Status: (b) (4) | Approve - Based on Previous History |
| | | Manufacturing and testing (b) (4) (b) (4) || 356h Status: (b) (4) | Approve - Based on Previous History |
| | | Manufacturing and testing (b) (4) (b) (4) || 356h Status: (b) (4) | Withhold - Not Ready |
| | | Manufacturing and testing (b) (4) (b) (4) || 356h Status: (b) (4) | Withdrawn |
| | | Celecoxib (b) (4) release testing || 356h Status: PendingCelecoxib (b) (4) release testing || 356h Status: Pending<br><br>LCP | Approve - Based on Previous History |
| Esteve Pharmaceuticals, S.A.Esteve Pharmaceuticals, S.A.<br><br>C/ de Sant Martí, 75-97 , Martorelles, Barcelona, Spain, 8107C/ de Sant Martí, 75-97 , | 3003121577 | Drug product manufacturer for Celecoxib and Tramadol, Tablets. Responsible for manufacturing, packaging, labeling, release testing (drug product and components) and stability testing. || 356h Status: | Approve - Based on Previous History |

| | | | |
|---|---|---|---|
| Martorelles, Barcelona, Spain, 8107 | | TCM | |
| (b) (4) | | (b) (4) Testing of Celecoxib-Tramadol, co-crystal API (drug substance). \|\| 356h Status: Pending (b) (4) Testing of Celecoxib-Tramadol, co-crystal API (drug substance). \|\| 356h Status: Pending<br><br>LCP | Approve - Based on Previous History |
| | | Testing of USP/NF excipients used in drug product manufacture of Celecoxib and Tramadol, Tablets \|\| 356h Status: PendingTesting of USP/NF excipients used in drug product manufacture of Celecoxib and Tramadol, Tablets \|\| 356h Status: Pending<br><br>LCP | No Evaluation Necessary |

**Biopharmaceutics: Adequate**

The biopharmaceutics review focused on the evaluation of the dissolution method and acceptance criterion for (b) (4) (tramadol and celecoxib) tablet and the bridging between the to-be-marked formulation and pivotal clinical formulations. Phase 3 clinical study (ESTEVE-SUSA-301 in USA) (b) (4) is the same as the to-be-marketed formulation. The dissolution profiles of tramadol HCl and celecoxib from exhibit stability batches were similar to the dissolution profiles of this Phase 3 clinical batch. In response to an IR, the Applicant accepted the Agency recommended Q= (b) (4)% in 15 minutes for both tramadol and celecoxib. Note that the Applicant has conducted some clinical trials (b) (4). The Applicant has provided comparative dissolution profiles between (b) (4) (b) (4) tablets to establish the bridging.

## C. Risk Assessment

| From Initial Risk Identification | | | Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking** | **Risk Mitigation Approach** | **Final Risk Evaluation** | **Lifecycle Considerations/ Comments** |
| Assay, Stability | Formulation<br>• Container closure<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | (b) (4) | Acceptable | None |

| | | | (b) (4) | | |
|---|---|---|---|---|---|
| Physical stability (solid state) | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site<br>• | M | | Acceptable | None |
| Content uniformity | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | | Not Acceptable | See manufacturing deficiencies. |
| Microbial limits | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | L | | Acceptable | |
| Dissolution | • Formulation<br>• Raw materials<br>• Process parameters<br>• Scale/equipment<br>• Site | M | | Acceptable | |

## D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

See drug product and manufacturing deficiencies below

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

Minor deficiency that should be addressed prior to a subsequent NDA resubmission (not an approvability issue):

- Regarding the submitted comparability protocol# (b) (4) we do not agree that is appropriate in this case. Please update the comparability protocol with a statement acknowledging that you will follow applicable regulations and guidance to determine the appropriate reporting category for the change. For additional information regarding the reporting category, see the FDA Guidances for Industry: "Changes to an Approved NDA or ANDA" (April 2004) and "Comparability Protocols for Human Drugs

and Biologics: Chemistry, Manufacturing, and Controls Information" (April 2016).

4. Labeling Deficiencies

Minor deficiency that should be addressed prior to a subsequent NDA resubmission (not an approvability issue):

- Include an equivalency statement for tramadol HCl indicating the strength in terms of the active moiety, tramadol. The equivalency statement should appear on the container label, carton labeling, and other labeling.

5. Manufacturing Deficiencies

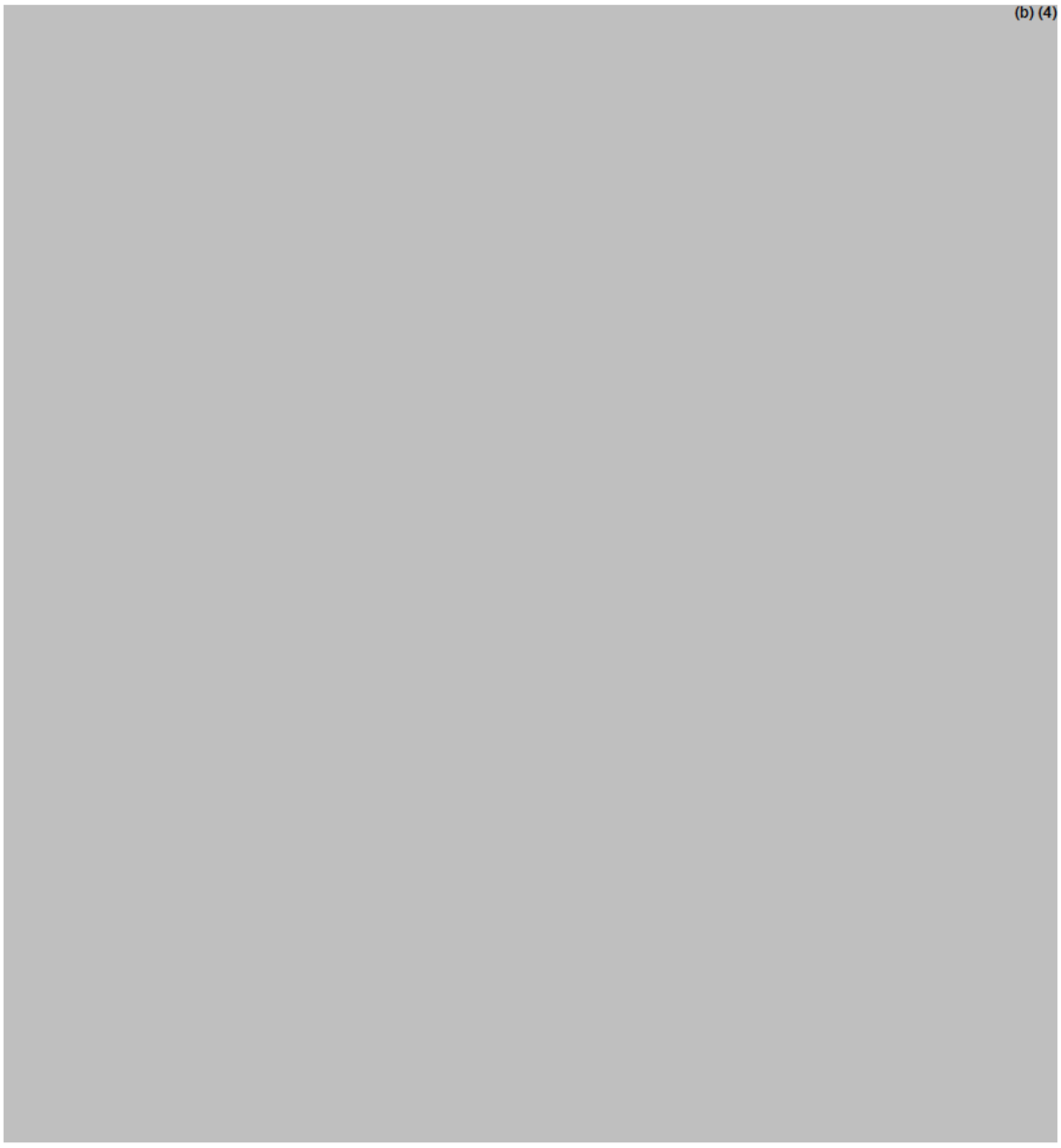
Major deficiency (approvability issue), that must be addressed prior to a subsequent NDA resubmission:

1. Our field investigator could not complete inspection of the (b) (4) manufacturing facility (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. Please notify us in writing when this facility is ready for inspection.

Minor deficiencies/recommendations (not approvability issues), that should be addressed prior to a subsequent NDA resubmission:

(b) (4)

(b) (4)



5. Biopharmaceutics Deficiencies

| None |
|---|

6. Microbiology Deficiencies

| None |
|---|

7. Other Deficiencies (Specify discipline, such as Environmental)

| None |
|---|

# QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Assessment Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | II | | (b) (4) | Active | | |
| | II | | | Active | | |
| | II | | | Active | | |
| | III | | | Active | N/A | Sufficient information in application |
| | IV | | | Active | N/A | Sufficient information in application |

### B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

| Document | Application Number | Description |
|---|---|---|
| NDA | 02028 | Ultram, Janseem Pharms |
| NDA | 021692 | Ultram ER, Valeant Pharms |
| NDA | 020998 | Celebrex, GD Searle |
| IND | 128177 | Co-crystal E-58425, LABORATORIOS DEL DR ESTEVE SA |

## 2. CONSULTS

| Discipline | Status | Recommendation | Date | Assessor |
|---|---|---|---|---|
| Biostatistics | | | | |
| Pharmacology/Toxicology | | | | |
| CDRH-ODE | | | | |
| CDRH-OC | | | | |
| Clinical | | | | |
| Other | | | | |

*Application Technical Lead Name and Date:*

*Renishkumar Delvadia, 01/22/2020*



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# CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

## 1.0 PRESCRIBING INFORMATION

**Assessment of Product Quality Related Aspects of the Prescribing Information:**

### 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Product Title in Highlights** | | |
| Proprietary name | (b) (4) | |
| Established name(s) | (celecoxib and tramadol hydrochloride) Tablets | Acceptable |
| Route(s) of administration | **oral use** | Acceptable |
| **Dosage Forms and Strengths Heading in Highlights** | | |
| Summary of the dosage form(s) and strength(s) in metric system. | Tablets: (b) (4) (b) (4) | Not acceptable: (b) (4) "celecoxib 56 mg and tramadol hydrochloride 44 mg" |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | N/A | |

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE AND ADMINISTRATION section** | | |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product) | (b) (4) | Not acceptable; (b) (4) (b) (4) (b) (4). The statement should be edited to "The dose of (b) (4) 56 mg/44 mg is 2 tablets every 12 hours." |

### Section 3 (DOSAGE FORMS AND STRENGTHS)

APPEARS THIS WAY ON ORIGINAL

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE FORMS AND STRENGTHS section** | | |
| Available dosage form(s) | coated tablets | Acceptable |
| Strength(s) in metric system | (b) (4) | Not acceptable: the statement should be "(b) (4) coated tablets contain 56 mg celecoxib and 44 mg tramadol hydrochloride" |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance | Celecoxib strength is based on celecoxib amount in co-crystal.<br><br>Tramadol hydrochloride strength is based on amount of salt in co-crystal; | Acceptable; USP exemption is applied since the previous tramadol product strengths are based on tramadol hydrochloride. |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting | The tablets are white to off-white elongated coated tablets debossed with "100" on one side and "CTC" on the other. | Acceptable; debossing "100" and "CTC" were found acceptable by DMEPA. |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | N/A |

| | | |
|---|---|---|
| For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package. | N/A | |

APPEARS THIS WAY ON ORIGINAL

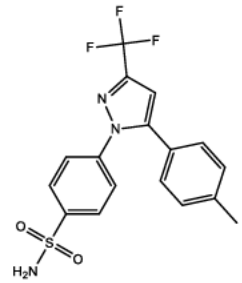
### 1.2.2 Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DESCRIPTION section** | | |
| Proprietary and established name(s) | (b) (4) | Acceptable; |
| Dosage form(s) and route(s) of administration | ((celecoxib and tramadol) Tablets | Acceptable. |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. | (b) (4) | Not acceptable: Equivalence statement needed for tramadol base; "(b) (4) coated tablets contain 56 mg celecoxib and 44 mg of tramadol hydrochloride (equivalent to XX mg of tramadol base) in a co-crystal structure." |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. | Inactive ingredients in the tablet are sodium lauryl sulfate, crospovidone, mannitol, sodium stearyl fumarate, talc, cellulose microcrystalline, copovidone and color mixture (polyvinyl alcohol partially hydrolized, titanium dioxide, polyethylene glycol and talc). | Acceptable. |
| For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. | N/A | N/A |

| | | |
|---|---|---|
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | N/A |
| Statement of being sterile (if applicable) | N/A | N/A |
| Pharmacological/ therapeutic class | an analgesic and opioid agonist and inhibitor (b) (4) | No acceptable; should be changed according to DAAP recommendation. |

APPEARS THIS WAY ON ORIGINAL

| | | |
|---|---|---|
| Chemical name, structural formula, molecular weight | Tramadol HCl:<br>The chemical name for tramadol hydrochloride is (1*RS*,2*RS*)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (b) (4)<br><br>The molecular weight of tramadol hydrochloride is 299.84.<br><br>Celecoxib:<br>The chemical name for celecoxib is 4-[5-(4-methylphenyl)- 3-(trifluoromethyl)-1*H*-pyrazol-1-yl] benzenesulfonamide and is a diaryl-substituted pyrazole. The molecular weight is 381.38 and it has the following chemical structure:<br><br>  | Tramadol: Not acceptable; Should be replaced with a (b) (4) structure.<br><br>Clarification needed (b) (4)<br><br>Celecoxib: Acceptable.<br><br>Co-crystal: Applicant will be asked to include information on molar ratios of individual components in a co-crystal structure. |
| If radioactive, statement of important nuclear characteristics. | N/A | N/A |

| | | |
|---|---|---|
| Other important chemical or physical properties (such as pKa or pH) | N/A | N/A |

**Section 11 (DESCRIPTION) Continued**

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| For oral prescription drug products, include gluten statement if applicable | Not provided | |
| Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity" | None | The Applicant will be asked to limit mentioning about co-crystal to Section 11. |

### 1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Available dosage form(s) | coated tablets | Acceptable |
| Strength(s) in metric system | (b) (4) | Not acceptable; statement should be "(b) (4) ((celecoxib and tramadol hydrochloride) Tablets) coated tablets contain 56 mg celecoxib and 44 mg tramadol hydrochloride." |
| Available units (e.g., bottles of 100 tablets) | (b) (4) | Not acceptable: correct NDC codes should in included Bottles of 30 tablets: NDC 68118-258-64 Bottles of 90 tablets: NDC 68118-258-70. |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | The tablets are to off-white elongated coated tablets debossed with "100 on one side and "CTC" on the other side | Acceptable |

| | | |
|---|---|---|
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | N/A | N/A |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | N/A | N/A |

**Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)**

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|

| | | |
|---|---|---|
| Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.) | Dispense in a tight container. | Acceptable |
| If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.” | N/A | Acceptable. |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. | Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F). [see USP Controlled Room Temperature]. | Acceptable. |
| Include information about child-resistant packaging | Does not claim “child-resistant closure” | Acceptable |

### 1.2.4 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

(b) (4)

DAAAP has been notified regarding this during the first labelling review meeting.

### *1.2.5* Manufacturing Information After Section 17 (for drug products)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Manufacturing Information After Section 17** | | |
| Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer | (b) (4) | Acceptable. |

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):**

None

**Acceptable.**

## 3.0 CARTON AND CONTAINER LABELING

**3.1 Carton Label**
**30 counts**


**90 counts**


### 3.2 Container Labeling

*(Copy/paste or refer to a representative example of a proposed carton labeling)*

*30 tablets:*


*90 tablets:*



1 Page of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

| Item | Information Provided in the NDA | Assessor's Comments about Container Labeling |
|---|---|---|
| Proprietary name, established name, and dosage form (font size and prominence | Tradename not included | Not acceptable |
| Dosage strength | 56 mg/44 mg | Acceptable |
| Route of administration | Not included | |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance | No Tramadol hydrochloride equivalency statement | Not acceptable; Equivalency statement needed for tramadol HCl. |
| Net contents (e.g. tablet count) | 30 or 90 counts | Acceptable |
| "Rx only" displayed on the principal display | Displayed | Acceptable |
| NDC number | Displayed | Acceptable |
| Lot number and expiration date | Displayed | Acceptable |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD. | Displayed | Acceptable |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use) | N/A | N/A |
| Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement. | N/A | N/A |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | N/A | N/A |
| Bar code | Displayed | Acceptable |

| Item | Information Provided in the NDA | Assessor's Comments about Carton Labeling |
|---|---|---|
| Name of manufacturer/distributor | Displayed | Acceptable |
| Medication Guide (if applicable) | Instruction to read the prescribing information. | Acceptable |
| No text on Ferrule and Cap overseal | N/A | N/A |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. | N/A | N/A |
| And others, if space is available | N/A | N/A |

**Assessment of Carton and Container Labeling: *Adequate***

## ITEMS FOR ADDITIONAL ASSESSMENT

***Overall Assessment and Recommendation:***

**Adequate with the following deficiency.**

**Include an equivalency statement for tramadol HCl indicating the strength in terms of the active moiety, tramadol. The equivalency statement should appear on the container label, carton labeling, and other labeling.**

*Primary Labeling Assessor Name and Date: Renishkumar Delvadia, 01/19/2020*

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

Renishkumar Delvadia

Digitally signed by Renishkumar Delvadia
Date: 1/23/2020 12:38:13PM
GUID: 5388ee7d000671ff7781f1835a3ff7b9

Julia Pinto

Digitally signed by Julia Pinto
Date: 1/23/2020 01:15:47PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

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# BIOPHARMACEUTICS

**Product Background:**

**NDA:** NDA-213426-ORIG-1

**Drug Product Name / Strength:** (b) (4) (tramadol and celecoxib) Tablet/100 mg (44 mg tramadol and 56 mg celecoxib)

**Route of Administration:** Oral

**Applicant Name:** ESTEVE PHARMACEUTICALS, S.A.

**Submission:**
Esteve Pharmaceuticals has submitted this NDA for (b) (4) (tramadol and celecoxib) Tablet/100 mg (44 mg tramadol and 56 mg celecoxib) for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Co-crystal of Tramadol and Celecoxib is a new Co-Crystal E-58425 composed by rac-Tramadol HCl / Celecoxib 44:56 (w/w).

The final dosing schedule in adults for Celecoxib and Tramadol Tablets is 200 mg every 12 hours as needed.

***Review Recommendation:*** **ADEQUATE**

***Review Summary:***
The biopharmaceutics review is focused on the evaluation of the dissolution method and acceptance criterion for (b) (4) (tramadol and celecoxib) tablet and the bridging between the to-be-marked formulation and pivotal clinical formulations.

**Dissolution Method and Acceptance Criterion: ADEQUATE**
The following dissolution method and acceptance criterion for the release of tramadol and celecoxib from the (b) (4) Tablet are approved:

| USP Apparatus | Speed (RPMs) | Medium/Temperature | Volume (mL) | Acceptance criterion |
|---|---|---|---|---|
| II (Paddle) | 75 | 0.1N HCl + 2% SLS | 1000 mL | Q = (b) (4) % in 15 minutes for both tramadol and celecoxib |

**Bridging of clinical formulations: ADEQUATE**
Phase 3 clinical study (ESTEVE-SUSA-301 in USA) was performed with the Co-crystal E-58425 100 mg coated tablet formulation ( (b) (4) batch #862110) which is same as the to-be-marketed formulation. The dissolution profiles of Tramadol HCl and Celecoxib from exhibit batches are similar to the dissolution profiles of the clinical batch.

**Biowaiver Request: Not requested**
Only one strength is developed.

**List of Submissions reviewed:**

| |
|---|
| Application 213426 - Sequence 0001 - 0001 (1) 05/15/2019 ORIG-1 /Multiple Categories/Subcategories |
| Application 213426 - Sequence 0007 - 0007 (7) 08/02/2019 ORIG-1 /Multiple Categories/Subcategories |

**Highlight Key Outstanding Issues from Last Cycle:** The Applicant was requested to submit the complete Tramadol HCl and Celecoxib dissolution data for the dissolution method development studies, for clinical batch 862110, and was requested to revise the dissolution acceptance criterion.

**Concise Description of Outstanding Issues Remaining:** None.

**Conclusion**
From biopharmaceutics perspective, NDA 213426 for (b) (4) (tramadol and celecoxib/44 mg tramadol and 56 mg celecoxib) is recommended for APPROVAL.

## BCS Designation

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

Pharmaceutical Development report suggests that Tramadol HCl belongs to BCS I and Celecoxib to BCS II. However, the Applicant has not claimed or requested any BCS classification for their drug product.

**Solubility**
The solubility of the Co-crystal E-58425 in different pH buffers is provided below.

**Table 1: Solubility of Co-crystal E-58425 in different pH buffers**

| | Co-crystal E-58425 Room temperature | |
|---|---|---|
| | **TRAMADOL** | **CELECOXIB** |
| 0.1N HCl | > 9 mg/mL | 0.0006 mg/mL |
| pH 4.5 | > 9 mg/mL | 0.0006 mg/mL |
| pH 6.8 | > 9 mg/mL | 0.001 mg/mL |
| pH 12 | 0.37 mg/mL | 0.29 mg/mL |
| | | (b) (4) |

Celecoxib is only soluble at pH 12, but at this pH the solubility of Tramadol is much lower (pka Tramadol HCl = 9.6) (b) (4)

**Table 2: Solubilities of Tramadol and Celecoxib in different media**

| | Co-Crystal of Tramadol and Celecoxib Room temperature | |
|---|---|---|
| | **TRAMADOL** | **CELECOXIB** |
| 0.1N HCl | > 9 mg/mL | 0.0006 mg/mL |
| | | (b) (4) |

**Dissolution:** Please see below.

## Drug Product

(b) (4) (Celecoxib and Tramadol, Tablets) is an immediate-release (b) (4) coated tablet for oral administration containing as drug substance a co-crystal of rac-tramadol HCI (racemic tramadol hydrochloride, also referred to as the cis-diastereoisomer of tramadol or +/- tramadol) and celecoxib. A 100 mg tablet of Celecoxib and Tramadol contains 44 mg of rac-tramadol HCI and 56 mg of celecoxib as the active pharmaceutical ingredients. The proposed indication is the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

The product and process development were conducted under a Quality by Design (QbD) paradigm to ensure desired product performance in terms of quality, safety, and efficacy. Dissolution was identified as one of the Critical Quality Attributes (CQAs) for the drug product.

The composition of the drug product is provided below.

**Table 3: Composition of (b) (4) Tablet**

| Name of the ingredients | Unit Composition % (w/w) | Unit Composition (mg) | Function | Amount per maximum Daily Dose (mg) | IIG Levels[1] (Oral tablet) (mg) | Quality standards |
|---|---|---|---|---|---|---|
| **Drug substance** | | | | | | |
| Celecoxib-Tramadol, co-crystal[2] | (b) (4) | 100.00 | Drug substance | 400.00 | -- | In-house |
| **Excipients** | | | | | | (b) (4) |
| Sodium lauryl sulfate | (b) (4) | | | | | |
| Crospovidone | (b) (4) | | | | | |
| Mannitol | (b) (4) | | | | | |
| Sodium stearyl fumarate | (b) (4) | | | | | |
| Talc | (b) (4) | | | | | |
| Microcrystalline Cellulose | (b) (4) | | | | | |
| Copovidone | (b) (4) | | | | | |
| Color mixture[4][5] | (b) (4) | | | | | |
| *Total* (b) (4) *coated tablet (mg)* | | | | | | (b) (4) |

## Dissolution Method and Acceptance Criterion

**Reviewer's Assessment: Adequate**

The biopharmaceutics review is focused on the evaluation of dissolution method and acceptance criterion for the release of tramadol and celecoxib from the (b) (4) Tablet.

**Proposed dissolution method and acceptance criterion**

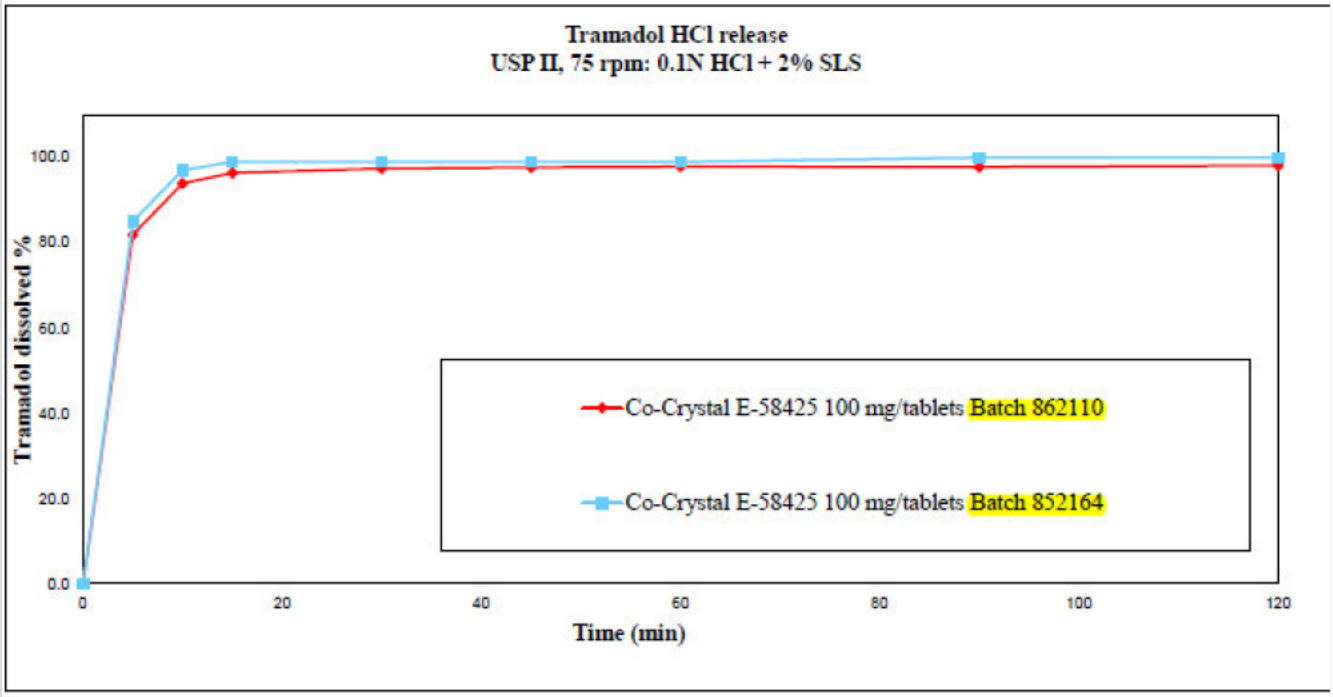
The following dissolution method and acceptance criterion were proposed:

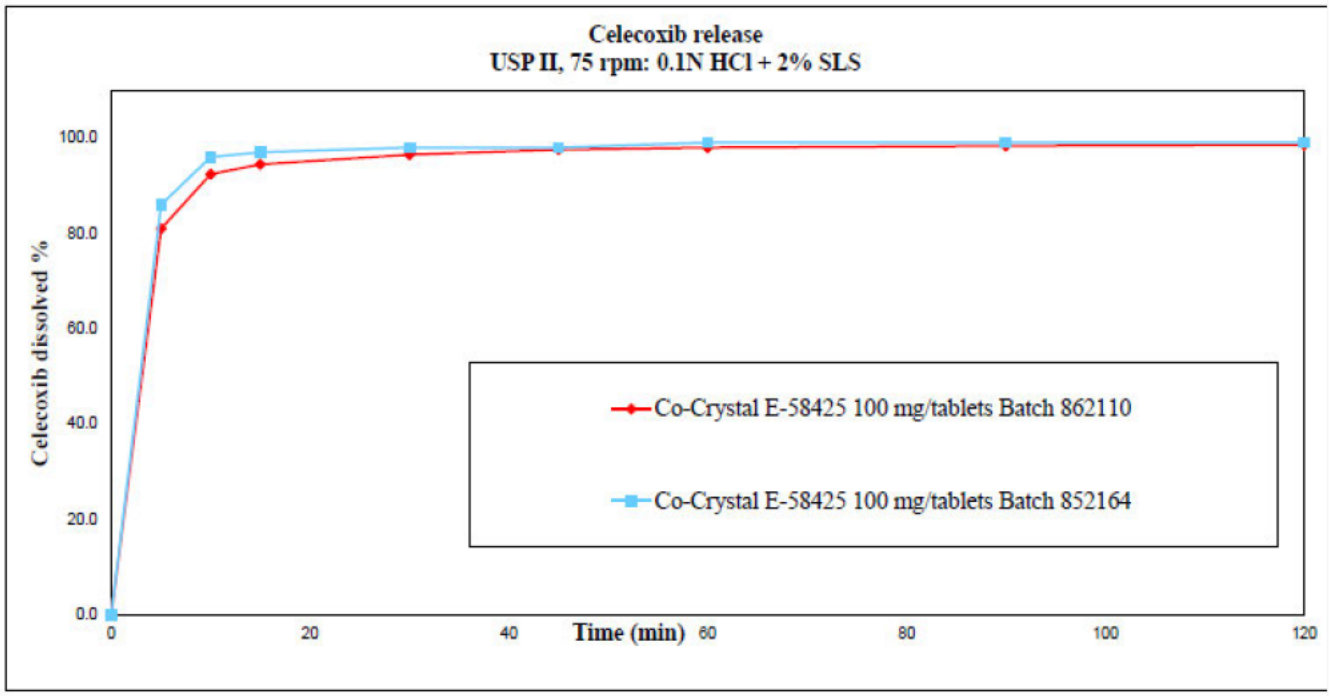
**Table 4: Dissolution Method for (b) (4) Tablet**

| USP Apparatus | Speed (RPMs) | Medium/Temperature | Volume (mL) | Acceptance criterion |
|---|---|---|---|---|
| II (Paddle) | 75 | 0.1N HCl + 2% SLS | 1000 mL | Q =(b) (4)% in(b) (4) minutes for both APIs |

In response to an IR (please see Appendix 1, IR1.2), the Applicant submitted complete dissolution profiles of Tramadol HCl and Celecoxib for Phase 3 clinical batch #862110 as shown below. Dissolution profiles of another batch (Batch #852164) was similar to the clinical batch showing batch-to-batch consistency. The dissolution data for 3 exhibit batches are also provided in Module 3.2.P.8.3 Stability Data; \\cdsesub1\evsprod\nda213426\0007\m3\32-body-data\32p-drug-prod\celecoxibtramadol-tablets\32p8-stab\stability-data.pdf).

. **Figure 1: Dissolution profile of (b) (4) Tablet Batch #862110**




The Applicant's proposed dissolution acceptance criterion is Q= (b) (4)% in (b) (4) minutes for both APIs. In response to an IR (IR1.3), the Applicant accepted the Agency recommended Q (b) (4)% in 15 minutes for both tramadol and celecoxib. The dissolution data for 3 exhibit batches comply with this tightened acceptance criterion.

**Dissolution method development**

(b) (4)

The details of the dissolution method development for the co-crystal tablet is provided in Module 3.2.P.2.4 Pharmaceutical Development (\\cdsesub1\evsprod\nda213426\0010\m3\32-body-data\32p-drug-prod\celecoxibtramadol-tablets\32p2-pharm-dev\pharmaceutical-development.pdf). In response to an IR (IR1.1), the Applicant provided complete dissolution data for the profiles in dissolution method development studies. Module 3.2.P.5.6 Justification of Specifications further justifies the dissolution method.

**Discriminating ability of the dissolution method**

The details of the discriminating ability of the proposed dissolution method is provided in Module 3.2.P.2.4 Pharmaceutical Development (\\cdsesub1\evsprod\nda213426\0010\m3\32-body-data\32p-drug prod\celecoxibtramadol-tablets\32p2-pharm-dev\pharmaceutical-development.pdf). In summary, batches containing drug substances with different PSD, ranging d(90) from (b) (4) µm were used to evaluate the discriminatory power of the proposed dissolution method.

**Figure 2: Tramadol HCl dissolution profiles for Co-crystal E-58425 (b) (4) mg tablets manufactured with drug substances with different PSD**

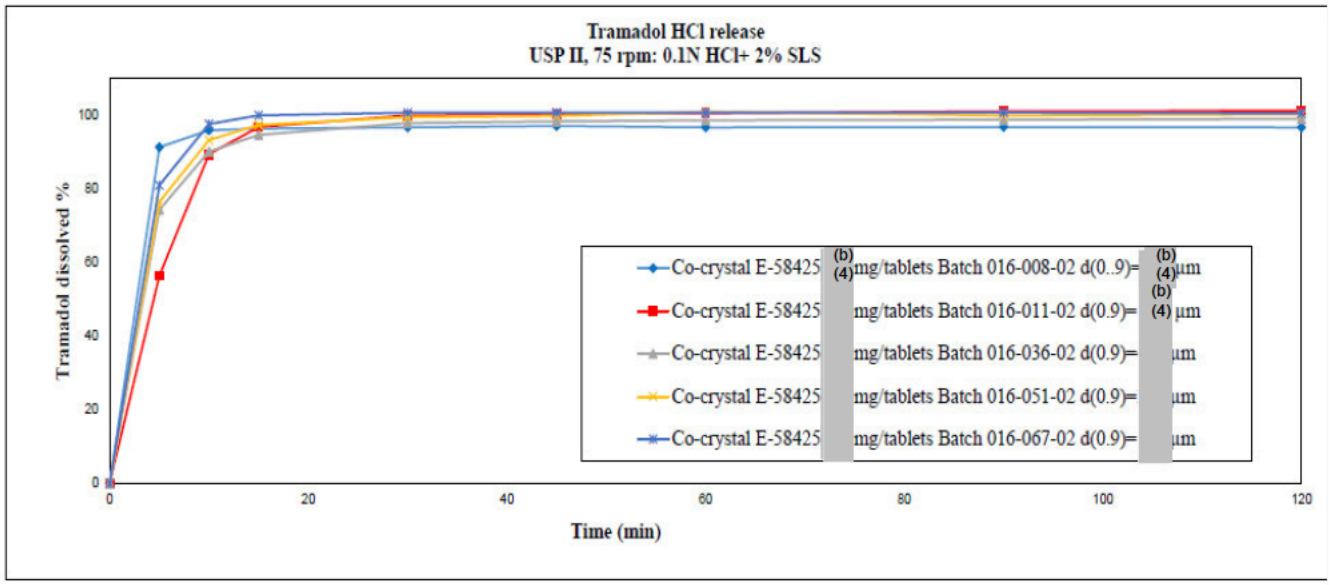
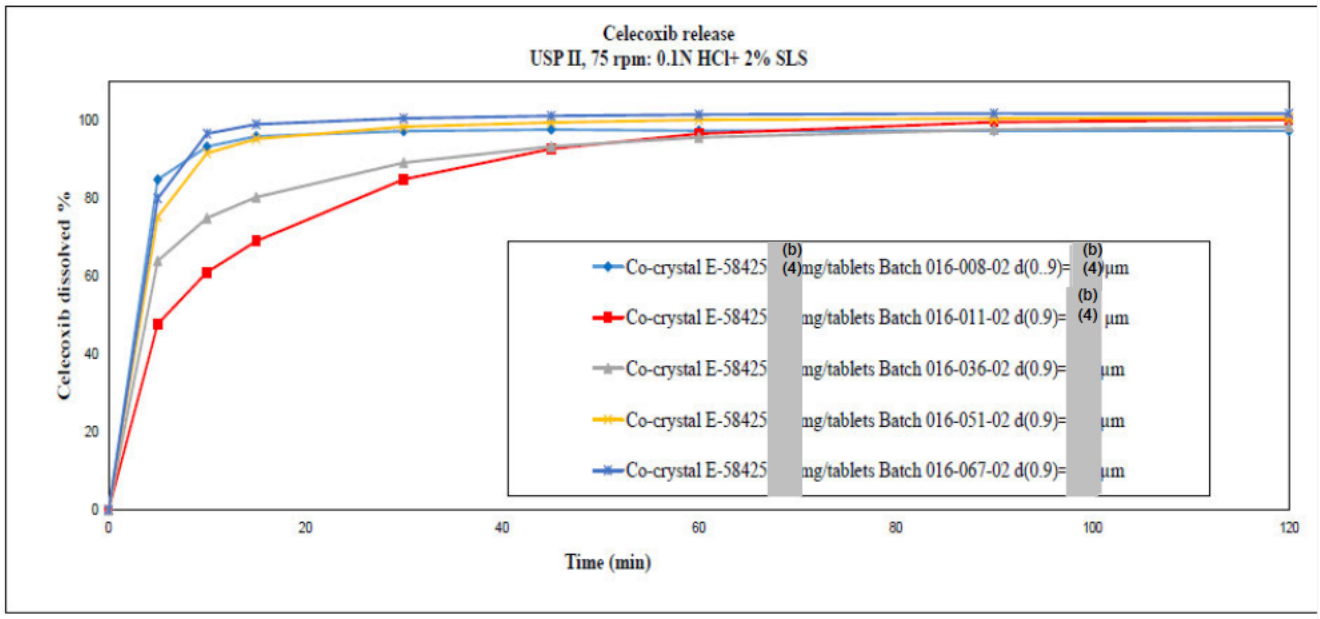



**Figure 2: Celecoxib dissolution profiles for Co-crystal E-58425 (b) (4) mg tablets manufactured with drug substances with different PSD.**




As can be seen in the figures above, different dissolution profiles were obtained for drug product containing drug substances Co-crystal E-58425 with different PSD showing that dissolution method has some discriminating ability. However, for tramadol, all dissolution profiles (n=6) met the proposed acceptance criterion. For celecoxib, co-crystals with particle sizes (b) (4) µm did not meet the acceptance criterion, showing that the proposed acceptance criterion is also sensitive to the particle size variation.

**Reviewer's assessment:**

- The Applicant has developed and validated a dissolution method using USP apparatus II. The dissolution method development report has been submitted. The proposed dissolution method has some discriminating ability towards particle size variation of the co-crystal. The proposed dissolution method is acceptable.
- The Applicant's proposed dissolution acceptance criterion is Q= (b) (4)% in (b) (4) minutes for both APIs. In response to an IR, the Applicant accepted the Agency recommended Q= (b) (4)% in 15 minutes for both tramadol and celecoxib.

## Bridging of Formulations

**Reviewer's Assessment: Adequate**

The Applicant initially conducted clinical trials using (b) (4) formulation as shown below.

| Clinical trials | Formula evaluated | Drug product batch number | Strength and details |
|---|---|---|---|
| ESTEVE-SACO4-103 (TAI-PO-692) | (b) (4) | 802659 (b) (4)<br>802660 (b) (4) | (b) (4) |
| ESTEVE-SACO4-102 (TAI-P0-584) | | 802660 | |
| ESTEVE-SACO4-104 (TAI-P1-585) | | 812513 | |
| ESTEVE-SACO4-105 | | 812513 | |
| ESTEVE-SACO4-201 | | 812516<br>812517<br>812518 | |

However, Phase 1 clinical study ESTEVE-SUSA-101 and Phase 3 ESTEVE-SUSA-301 in USA were performed with the Co-crystal E-58425 100 mg (b) (4) tablets formulations (b) (4) (b) (4) which is same as the to-be-marketed formulation (composition shown in table 3). The clinical batch #862110 was used in both clinical studies as shown below. The dissolution profiles of Tramadol HCl and Celecoxib from this clinical batch is presented in Figure 1. The dissolution profiles of exhibit batches are similar to this batch, both meeting the dissolution acceptance criterion.

The Applicant has provided comparative dissolution profiles between (b) (4) (b) (4) tablets as shown below which shows similar dissolution profiles.

**Figure 3: Dissolution profile comparison of Tramadol in Co-crystal E-58425 100 mg (b) (4) (b) (4) tablets 0.1N HCl + 2% SLS**

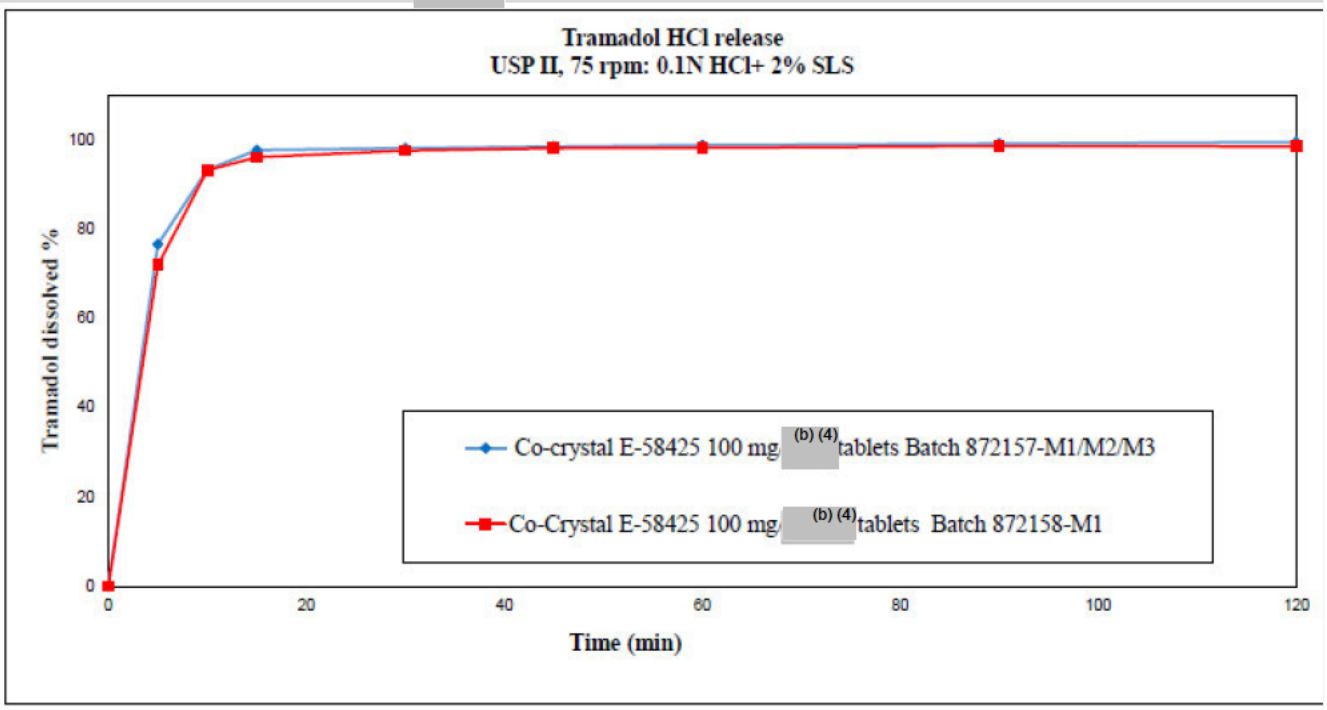
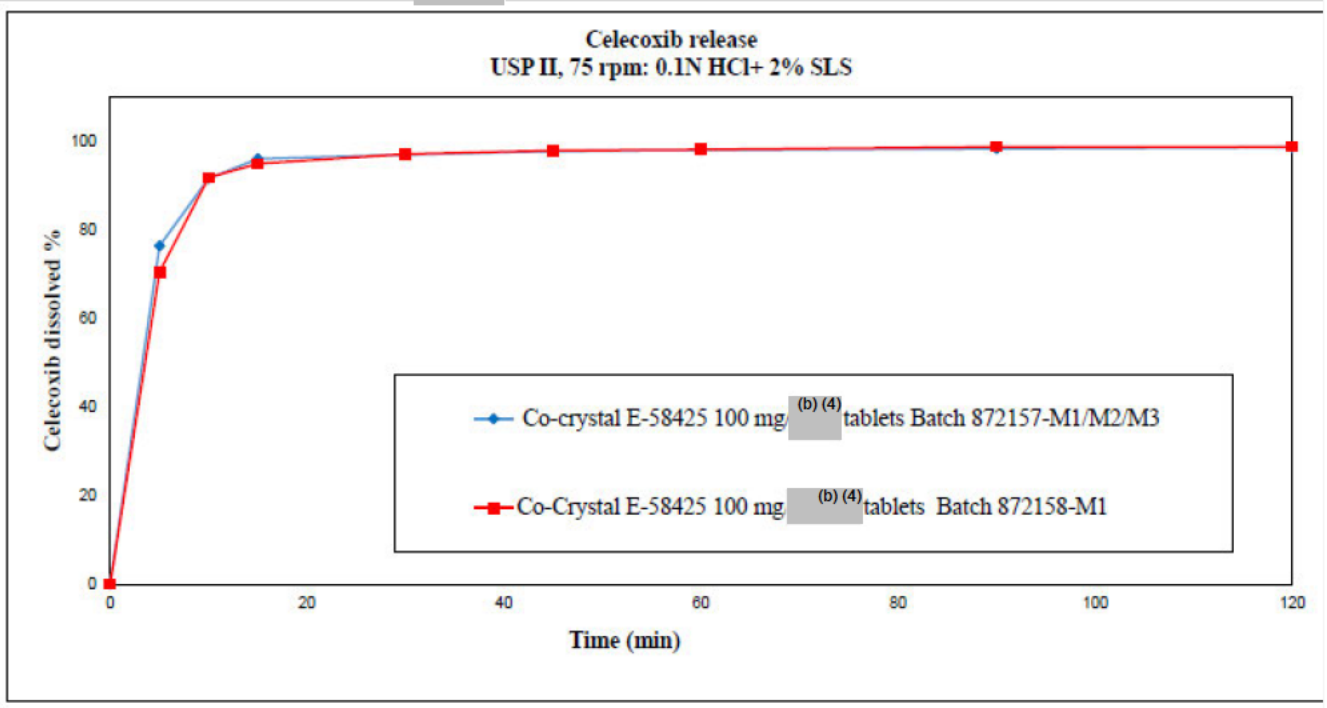



**Figure 4: Dissolution profile comparison of Celecoxib in Co-crystal E-58425 100 mg (b) (4) (b) (4) tablets 0.1N HCl + 2% SLS**



**Biowaiver Request**

**Reviewer's Assessment:** The Applicant has not requested any biowaiver. There is only one strength of the drug product.

**Conclusions and recommendation**

From Biopharmaceutics perspective, NDA 213426 is recommended for APPROVAL.

# *Appendix 1*

***The Information Request conveyed to the Applicant during the review process***

**Information Request 1 (IR 1)**

(b) (4)

***Primary Biopharmaceutics Reviewer Name: Kalpana Paudel, Ph.D.***

***Secondary Reviewer Name: Hansong Chen, PharmD, Ph.D.***

Kalpana Paudel

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Date: 1/17/2020 03:17:05PM
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Hansong Chen

Digitally signed by Hansong Chen
Date: 1/17/2020 03:26:29PM
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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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RENISHKUMAR R DELVADIA
01/27/2020 06:52:37 PM