

**Initial Quality Assessment
ONDQA/ Division of Pre-Marketing Assessment I**

NDA: 22-266
OND Division: Division of Anesthesia, Analgesia and Rheumatoid Products (HFD-170)
Applicant: BioDelivery Sciences International
Legal Basis for Submission: 505(b)(2) (relying approved NDA: Actig NDA 20-747)
Status Date: 31-OCT-2007 (Letter date 28-OCT-2007)
PDUFA Date: 10-MAY-2007
Proposed Proprietary Name: _____ (BEMATM Fentanyl) **b(4)**
Established Name: Fentanyl
Dosage form and strength: Mucoadhesive rectangular strip, 200, 400, 600, 800, and 1200 µg
Route of Administration: Buccal transmucosal
Indications: For the management of pain in cancer patients who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.

Fileability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer

Time Goals	
<i>Activity</i>	<i>Date</i>
NDA 22-266 Clock Date (Stamp Date)	31-OCT-2007
Initial Quality Assessment in DFS	03-DEC-2007
Filing decision "Day 45" Meeting Date	14-DEC-2007
60-day filing date	28-DEC-2007
Filing review issues sent to applicant "Day 74"	12-JAN-2008
Mid-cycle meeting "Month 5"	To be defined by DAARP
Final Chemistry Review "Month 8"	27-JUN-2008
DAARP Goal Date	To be defined
10 months-PDUFA	29-AUG-2008

Consults/ CMC Related Reviews	
<i>Discipline/ Division Consulted</i>	<i>Comment</i>
OCPB	--
CDRH	N.A.
EA	Categorical exclusion granted under 21 CFR§25.31
EES	EER submitted on 14-NOV-2007 ^(a)
DDMAC	Labeling ^(b)
DMETS	Adequacy of proposed drug product tradename ^(c)
Methods Validation	Revalidation by Agency laboratories may be requested after test methods are finalized.
Microbiology	-- (Unless DAARP policy systematically has Micro Consults.)
Pharm/Tox	-- (Structural alerts have been pointed out to Pharm/Tox.)

DDMAC = Division Drug Marketing, Advertising, and Communications; **CDRH** = Center for Devices and Radiological Health; **DMETS** = Division of Medical Errors and Technical Support; **EER** = Establishment Evaluation Request; **EES** = Establishment Evaluation System; **N.A.** = Not Applicable; **OCPB** = Office of Clinical Pharmacology and Biopharmaceutics; **OMP** = Office of Medical Policy; **ODS** = Office of Drug Safety.

^(a) See attachment

^{(b), (c)} Originator: Kimberly Compton, PM, DAARP. Multidisciplinary Review.

Drug Product (DP)

- The commercially available drug product, BEMA™ Fentanyl is presented as a buccal mucoadhesive strip available in five dose strengths: 200, 400, 600, 800, and 1200 µg fentanyl free base.
- The drug product is a flexible, flat, bilayer rectangle with round corners, pink on one side and white on the other. The white backing layer does not contain drug substance and it minimizes drug release into the oral cavity, maximizing transmucosal diffusion. The dose unit dissolves within 15 to 30 minutes.
- Each dose strengths contains Fentanyl Citrate (active) _____ Water _____ Propylene Glycol _____ Sodium Benzoate _____, Methylparaben _____ Propylparaben _____ Ferric Oxide _____ Citric Acid _____, Vitamin E _____, Monobasic Sodium Phosphate _____, Sodium Hydroxide _____, Tribasic Sodium Phosphate _____ Polycarbophil _____, Hydroxypropyl Cellulose _____, Hydroxyethyl Cellulose _____ Carboxymethylcellulose _____, Titanium Dioxide _____ Saccharin Sodium _____, and Peppermint Oil _____ All excipients meet compendial requirements and are listed in CDER's "Inactive Ingredients in FDA Approved Products Database" for buccal, sublingual, or oral administration.
- The concentration of drug substance within the mucoadhesive layer is the same for all product strengths. The fentanyl dose is determined by the dose unit size, defined by surface area.
- Each BEMA™ Fentanyl dose unit is marked with a product strength identifier on the white backing side and packaged in a child-resistant, _____ foil, _____ package. The different dose strengths (200, 400, 600, 800, and 1200 µg fentanyl free base) differ in size and color packaging.
- Manufacturing process simplified overview is attached. Manufacturing development provided.
- DP specifications include appearance (color), identification (HPLC and UV-Vis), assay (HPLC; Fentanyl range _____ Purity (HPLC; Impurity _____ NMT _____, impurity _____ NMT _____ Unknown impurity (individual NMT _____, and Total NMT _____), content uniformity (USP <905>), unit weight, pH (6.5-8.5), dissolution (NLT _____ at 60 min), water content _____, and microbial limits (USP <61>).
- Adequate information to assign a shelf-life. Stability data available from 26 lots (22 represent commercial formulation, 4 lots were formulated at different pHs). Seventeen lots of the commercial formulation have 18 month data. Eighteen lots have 6 months of stability data at the accelerated storage condition.

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Critical Issues: (This is not an exhaustive list of critical issues.)

- DMF _____ was found adequate. Fentanyl citrate (DS) manufactured by _____ is acceptable (CMC Review date 22-Nov-2004) _____ the DP of NDA 20-747. Annual reports after 2004 should be checked, in particular to the adequacy of impurity levels. b(4)
- Process impurities properly evaluated?
- Adequacy of the DP specification for:
 - “Unknown Impurity NMT” _____ conformity to ICH guidances. b(4)
 - Conventional dissolution testing as used for oral dosages forms
- Acceptability of the DP purity acceptance criteria based on safety demonstrated in clinical lots.
- Adequacy of analytical stability indicating testing procedures (DS and DP).
- Adequacy of the container-closure material in contact with DP. Product contact layer, _____ manufactured by _____, claimed to comply with 21 CFR §177 –Indirect Food Additives: Polymers Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces 177.1480 _____ b(4)
- Adequacy of proposed shelf life under proposed usage. b(4)

Comments and Recommendation:

The NDA is considered Fileable from a CMC perspective.
The other critical issues previously listed, will be evaluated as part of the review.

	Xavier Ysern, PhD	Review Chemist	ONDQA/ DPA I/ Branch II	29-Nov-2007
Init.	Ali Al-Hakim, PhD	Branch Chief	ONDQA/ DPA I/ Branch II	

Attached:

	<u>Page</u>
(A) DS and DP manufacturing facilities and EER summary report (3 pages)	5
(B) DS Specifications (1 page)	8
(C) DP Manufacture and Specifications (1 page)	9

Attachment A (list of facilities involved in DS and DP manufacture, DMF listing, and EES summary report)

Facilities involved in DS and DP Manufacture, Release and Stability Testing, and Packaging		
<i>Site/Address</i>	<i>CFN</i>	<i>Responsibility</i>
Drug Substance (Fentanyl Citrate)		
[REDACTED]	[REDACTED]	[REDACTED]
Drug Product (BEMA™ Fentanyl, 200, 400, 600, 800, and 1200 µg) Avea Drug Delivery Systems, Inc. (Aveva) Finished Product: Manufacturing 3250 Commerce Parkway Miramar, FL 33025		

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Contact: Mary Gonzales,
 Vice President Quality and Regulatory Affairs
 Telephone: 954-624-1224, fax: 954-430-3390,
 e-mail: mary.gonzales@avevadds.com.

CFN: Central File Number.

List of referenced Drug Master Files (DMF's)		
<i>Name and address</i>	<i>Component</i>	<i>DMF #</i>
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
*** [REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

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14-NOV-2007

FDA CDER EES

Page 2 of 2

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: _____ AADA _____
Responsibilities: _____

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Profile: CSN OAI Status: NONE

Estab. Commer: _____

b(4)

(on 14-NOV-2007 by X. YSERN () 301-796-2410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-NOV-2007				YSERNX

Attachment B (Drug Substance Specifications)

Fentanyl Citrate Specifications		
<i>Test</i>	<i>Acceptance Criteria</i>	<i>Analytical Procedure</i>
Appearance	White to off-white powder	Visual, STP 101
Identification, IR	Compares to standard	STP 141 USP <197K>
Identification, UV	Compares to standard	USP <197U>
Loss on Drying	≤ 0.50 %	USP <731>
Residue on Ignition	_____	USP <281>
Heavy Metals	≤ 0.002 %	USP <231>
Ordinary Impurities	_____	USP <466>, TLC
Assay (Dry Basis) Titration	98.0-102.0 %	USP Monograph
Assay	98.0-102.0 %	HPLC, STP 519
Purity and Related Substances ^a (% w/w):		HPLC, STP 519
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Unknown Related Substances (Each)	_____	
Total Related Substances	_____	

^a Related substances' chemical structures shown below.

b = _____

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Fentanyl Citrate Related Substances	
<i>Compound</i>	<i>Structure</i>

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Xavier Ysern
12/19/2007 01:40:00 PM
CHEMIST

Ali Al-Hakim
12/19/2007 04:35:31 PM
CHEMIST