All opioid labels have warnings regarding co-ingestion with alcohol, based on the additive effects of the two substances; however stronger warnings and/or non-approval of a drug could result from findings of significant dose dumping.

2.5 Presubmission Regulatory Activity

BEMA Fentanyl has been developed under IND 62,864.
A **Pre-IND meeting** was held with the Division on May 16, 2001 with Atrix Laboratories, the original Sponsor. The proposed indication for BEMA Fentanyl at that time was the [redacted] b(4)

The advice provided by the Division regarding the clinical development plan included the following:

- The pharmacokinetics of the final formulation must be assessed after chewing followed by immediate swallowing, and after prolonged retention in mouth.
- Extractability of fentanyl from the to-be marketed formulation must be assessed.
- Bioavailability in cancer patients with oral mucositis should be evaluated.
- Oral dosage formulations for home use must be childproof.
- A Risk Management Program will have to be implemented at the time of NDA approval in order for the product to be safely used by the intended population and to minimize risks of misuse and exposure related to the unintended population.
- Abuse liability issues must be studied.
- BEMA Fentanyl would be Schedule II.

A **Type-C meeting** was held with BDSI (the current Applicant) January 26, 2005. BDSI licensed the technology from Atrix Laboratories. BDSI clarified that the indication they were seeking was for [redacted] They expected patients to have [redacted] of exposure b(4)
to the product. The advice provided by the Division regarding the clinical development plan included the following:

- The Agency confirmed that by limiting the indication to the treatment of BTP in patients with malignancies, no reproductive toxicity or carcinogenicity studies would be required;
- The controlled substances staff (CSS) agreed that a clinical abuse liability study is not needed if the sponsor is accepting a Schedule II placement for BEMA Fentanyl;
- A bioequivalence study should assess the effects of mucositis on the PK of BEMA Fentanyl;
- The study design and endpoints proposed for the Phase 3 clinical efficacy study, FEN-201, appear appropriate;
- The Division agreed that a 505(b)(2) application referencing approved fentanyl products may be appropriate, and provided guidance to that end;
- The Division agreed that a single Phase 3 efficacy trial may be sufficient to support the efficacy of BEMA fentanyl;

- The safety database should consist of 300-500 patients exposed for 6 months, but the Division would consider three months if the sponsor provides acceptable justification;
- The Risk Management Plan (RMP) should address the safety, abuse liability, chemical extraction, and patient education concerns of the Agency as reflected in the minutes.
- Extensive comments were provided regarding abuse liability determination, including the conduction of extractability studies.

Correspondence from the Agency July 5, 2005:

- Confirmed that safety database of 300-500 evaluable patients (excluding healthy PK subjects), at least 100 of whom were treated for at least 3 months would be acceptable.

Teleconference August 31, 2006:

- Agency advised that the first dose of BEMA Fentanyl in studies FEN-201 and 202 should be administered in the **investigator's office rather than unsupervised at home, in order to monitor patient's** reaction to first exposure.

Type C Meeting September 15, 2006:

- The primary endpoint (SPID30) for the pivotal studies, using the last observation carried forward (LOCF) convention and the size of the safety database (at least 300 patients) were agreed. The Division also requested that information be provided in the study report on the randomization schedule(s) used in FEN-201.
- The RiskMAP should be complete when submitted with the NDA package.

Pre-NDA Meeting June 28, 2007:

- The Division requested a cumulative responder analysis be performed to evaluate the number of subjects achieving reduction in pain across multiple cutoffs. All subjects who drop out of the study should be considered non-responders.
- A cutoff of 5% for adverse events is acceptable for labeling; however tables with cutoffs of 1% should be submitted in the NDA. There should be two tables for adverse events; one for events occurring during titration only and one for events occurring during the double-blind period of FEN-201 and the long-term treatment period of FEN-202.
- Any report in a child or adolescent, whether or not the exposure was intended or unintended, and regardless of outcome, any medication error should be submitted to FDA as a Postmarketing 15-day alert report.
- The titration scheme proposed by the sponsor will require a detailed rational and will be reviewed by the Agency.
- [redacted]

b(4)

- Additional information on abuse liability assessment should be provided in the NDA. Specifically, cases of abuse, overdose, missing, lost, or stolen drug should be described.

2.6 Other Relevant Background Information

BEMA Fentanyl is not approved in any other country; therefore there is no additional relevant background information.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINE

3.1 CMC (and Product Microbiology, if Applicable)

BEMA Fentanyl is an oral transmucosal form of the potent opioid analgesic, fentanyl citrate, intended for application to the buccal mucosa. It uses the BEMA™ (BioErodible MucoAdhesive) bilayer delivery system which is comprised of water-soluble polymeric films. Each dose unit consists of a pink bioadhesive layer bonded onto an opaque white backing layer. The active ingredient, fentanyl citrate, is incorporated into the bioadhesive layer, which adheres upon contact (<5 seconds) with the moist buccal mucosa. The backing layer acts as a barrier to minimize diffusion of fentanyl into the saliva and accumulation of drug in the oral cavity, thus promoting delivery of fentanyl into mucosal tissues. BEMA fentanyl dissolves within 15 to 30 minutes after application.

Interested readers are referred to Dr. Xavier Ysern's review for a complete discussion of CMC issues.

3.2 Animal Pharmacology/Toxicology

The safety profile and local tolerance of BEMA Fentanyl has been investigated in the formulation screening studies, the 28-day, repeat-dose toxicity study, and the single-dose, local tolerance studies. In addition, the safety profile of fentanyl has been previously investigated in a number of studies in various animal species as reported in the literature.

In the non-GLP formulation screening studies and the GLP local tolerance studies following a single-dose administration, no new systemic adverse effects were noted and no significant local irritation was attributed to BEMA Fentanyl administration.

In the 28-day BEMA Fentanyl study in dogs, treatment-related effects included decreased activity, abnormal gait and stance, excessive salivation, tremors, emesis, decreased body weight and weight gain, decreased food consumption, and decreased WBC parameters. There were no definitive differences in toxicity noted based on the pH of the discs (pH 6.5, 7.25, or 8.5) and no treatment-related local irritation lesions noted in samples of oral mucosa histopathologically examined.

A complete review of the preclinical development of BEMA Fentanyl has been performed by Dr. Gary Bond, and those interested in further detail are referred to that review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The sources of clinical data for this review include the clinical study reports submitted by the Applicant and information from the labeling of related products.

4.2 Tables of Clinical Studies

Table 2: Summary of Pharmacokinetic Studies

Protocol	Title	Objectives	Population, Duration	Dose	Number of Subjects
FEN-104	A Single Center, Randomized, Single-Dose, Crossover, Pharmacokinetic Study Comparing the Bioavailability of BEMA™ Fentanyl (AL-3701.02) to a Reference Oral Transmucosal Fentanyl Citrate (Actiq®) In Healthy Volunteers	Evaluate PK for early formulation	Volunteers, single dose (repeated)	250 µg BEMA Fentanyl (early formulation) Actiq 200 µg	12 [a]
FEN-107	A Comparison of the Pharmacokinetics of Three Different Formulations of BEMA Fentanyl with Actiq	Select pH buffered formulation, compare PK with Actiq	Volunteers, single dose	800 µg BEMA Fentanyl or Actiq	12
FEN-109	An Evaluation of Adherence and Fentanyl Absorption from BEMA™ Discs Under a Range of Conditions	Evaluate effect of heat on PK, evaluate transdermal absorption	Volunteers, single dose	400 µg [b] 1200 µg [c]	6
FEN-110	An Evaluation of the Single Dose Pharmacokinetics of BEMA™ Fentanyl	Evaluate dose-linearity and exposure across dose range	Volunteers, single dose	200, 600, 1200 µg	12
FEN-112	An Evaluation of the Multiple Dose Pharmacokinetics of BEMA™ Fentanyl in Normal Healthy Volunteers	Evaluate consistency of PK single for multiple doses	Volunteers, single and multiple dose	600 µg	12
FEN-113	An Evaluation of Fentanyl Absorption from the BEMA™ Delivery System in the Presence of Mucositis	Evaluate effect of mucositis on PK	cancer patients, single dose	200 µg	14
FEN-114	An Evaluation of the Absolute Bioavailability and Transmucosal Absorption of Fentanyl from the BEMA Delivery System	Evaluate absolute bioavailability and effect of gender	Volunteers, single dose	800 µg	12
Total [a]					68

a Total does not include 12 subjects from FEN-104 who used a different formulation.
b Buccal dose
c Transdermal dose

Source: BEMA Fentanyl NDA, Clinical Overview, P.9

Table 3: Summary of Clinical Studies Supporting Findings of Efficacy and Safety

Study	Title	Brief Description
FEN-201	A Double-blind, Placebo-controlled Evaluation of the Efficacy, Safety and Tolerability of BEMA™ Fentanyl in the Treatment of Breakthrough Pain in Cancer Subjects	80 opioid-tolerant subjects with cancer and breakthrough pain, initial titration to a tolerated, efficacious dose of BEMA Fentanyl, randomized to a cross-over sequence of 6 active doses and 3 placebo doses. Efficacy assessed in primary and secondary endpoints.
FEN-113	An Evaluation of Fentanyl Absorption from the BEMA™ Delivery System in the Presence of Mucositis	14 volunteers with cancer, 7 of whom have mucositis with pain, given a single open-label dose. Primary endpoint of pharmacokinetics. Secondary assessment of mucositis pain.
FEN-202	An Open-label, Long-term Treatment Evaluation of the Safety of BEMA™ Fentanyl Use for Breakthrough Pain in Cancer Patients on Chronic Opioid Therapy	220 opioid-tolerant subjects with cancer pain, either as continuation therapy from study FEN-201 or de-novo titration. Efficacy inferred from secondary assessments.

Source: BEMA Fentanyl NDA, Integrated Summary of Efficacy, p. 1

4.3 Review Strategy

For this 505(b)(2) application, the Applicant submitted a single adequate and well-controlled efficacy study (FEN-201). The Applicant also cited findings of efficacy for Actiq (oral transmucosal fentanyl citrate) as evidence of the efficacy of BEMA Fentanyl.

Dr. Joan Buenconsejo of the Division of Biometrics II reanalyzed and **confirmed the Applicant's** analysis of efficacy for the primary endpoint. The interested reader is referred to her review for a detailed description of the analysis and findings.

The primary electronic datasets used for the efficacy analyses were those containing data for Study FEN-201.

Data from studies FEN-201, FEN-202, and FEN-113 were utilized in the integrated safety analysis. The safety review focused on adverse events, particularly deaths, serious adverse events, and morbidity related to the application site of the drug. The Integrated Summary of Safety (ISS) datasets that were used for the safety review are the following:
AF_AE.xpt, AF_CANC.xpt, AF_DISP.xpt, AF_DOSE.xpt, AF_EXP.xpt, AF_MED.xpt, AF_MOUTH.xpt, AF_PHYS.xpt, AF_VITAL.xpt, FORMATS.xpt, MPF.xpt.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) was consulted to inspect two study sites in the United States. The selection of sites was based on the enrollment of study subjects. These inspections are pending at this writing.

4.5 Compliance with Good Clinical Practices

At this writing, inspection reports from DSI are pending.

4.6 Financial Disclosures

The Applicant submitted Form FDA 3454. There were no disclosed financial arrangements with clinical investigators that required further consideration.

5 CLINICAL PHARMACOLOGY

Refer to the complete Biopharmaceutics review performed by Dr. David Lee for detail regarding the clinical pharmacology aspects of BEMA Fentanyl.

5.1 Pharmacokinetics

Following buccal application, Bema Fentanyl was rapidly absorbed and the absolute bioavailability was 71%. This absolute bioavailability study also demonstrated similar pharmacokinetics in the subsets of 6 male and 6 female adult normal volunteers.

The absorption pharmacokinetics of fentanyl from BEMA Fentanyl is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Based on the absolute bioavailability study, approximately 51% of the total dose is rapidly absorbed from the buccal mucosa. The remaining 49% of the total dose is swallowed with the saliva and then slowly absorbed from the GI tract. About 1/3 of this amount (20% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available.. A unit dose if chewed and swallowed, will likely result in lower peak concentrations and lower bioavailability than when consumed as directed.

In a study that compared the relative bioavailability of BEMA Fentanyl and Actiq (oral transmucosal fentanyl citrate [OTFC]) in 12 adult normal volunteers, the rate and extent of fentanyl absorption were greater with BEMA Fentanyl (approximately 60% greater maximum plasma concentration and 40% greater exposure). Table 4 below illustrates this comparison.

Table 4
Fentanyl Plasma Pharmacokinetic Parameters in Healthy Adult Subjects Receiving Single Doses of TRADENAME or Actiq

Pharmacokinetic Parameter*	TRADENAME (800 mcg)	Actiq (800 mcg)
C_{max} (ng/mL)	1.67 ± 0.75	1.03 ± 0.25
AUC_{inf} (hr·ng/mL)	14.46 ± 5.4	10.30 ± 3.8
T_{first} (min)	9.0 ± 4.8	13.2 ± 10.8
T_{max} (hr)	1.00 (0.75 – 4.00)	2.00 (0.50 – 4.00)

* Data for T_{max} presented as median (range); other data are presented as mean ± SD

Source: Proposed label for BEMA Fentanyl

In another study, dose proportionality across the range of the available dosage strengths of BEMA Fentanyl was demonstrated in a balanced crossover design comparing fentanyl plasma concentrations in three dosage strengths (200, 600, and 1200 mcg) in adult normal volunteers

(n=12).

b(4)

b(4)

Source: Proposed BEMA Fentanyl Label

The effect of oral mucositis (Grade 1) on the pharmacokinetic profile of Bema Fentanyl was studied in a group of cancer patients with (N=7) and without (N=7) oral mucositis. A single 200 mcg unit was administered, followed by sampling at appropriate intervals. Application of BEMA Fentanyl on an active site of mucositis was associated with decreases in the C_{max} and AUC_{inf} that are not likely to be clinically relevant.

During the BEMA Fentanyl development program, there were no drug-drug interaction studies, however the metabolism of fentanyl has been well documented. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by CYP3A4 isoform. The concomitant use with strong CYP3A4 inhibitors or the weak CYP3A4 inhibitor cimetidine may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression.

The concomitant use of BEMA Fentanyl with potent CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of BEMA Fentanyl

5.2 Pharmacodynamics

Pharmacological effects of opioid agonists are well known and include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to