Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☒ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Actiq, N 20-747

3. **Is this application for a drug that is an "old" antibiotic** (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☒

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☒

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☒

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☒ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☒ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

***NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☒ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12. **Yes.**

8. **Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a change in the dosage from from an oral transmucosal lozenge on a stick, to a bioerodible oral mucoadhesive patch.**

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☒

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☒

11. Is the application for a duplicate of a listed drug whose only difference is **that the rate at which the product's active ingredient(s) is absorbed or made** available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES ☐ NO ☒

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☒ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☒ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Actiq, Non-clinical.

Was this listed drug product(s) referenced by the applicant? (see question # 2)
YES ☒ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☒ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☒ NO ☐

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration
N 20-747		**M-63**	**2-6-10**

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/s/

Kimberly Compton
8/21/2008 06:42:01 PM
CSO

Compton, Kimberly

From: Compton, Kimberly
Sent: Wednesday, June 04, 2008 3:13 PM
To: 'David T. Wright'
Cc: Compton, Kimberly
Subject: Agency Attendees for 6-3-08 TC and labeling item

Thanks Dave.

We had on our side:

Myself
Sharon Hertz, MD, Deputy Director
Xavier Ysern, PhD, Chemistry Reviewer
Ali Al-Hakim, PhD, Chemistry Branch Chief
Ellen Fields, MD, Medical Officer

In addition, we have begun to take a an early look at the revised labeling you sent us, in particular in response to our request about revisions to the AE section, and we have the following comment.

> We acknowledge your response to our request regarding the presentation of adverse events in the product label. Table 1 is acceptable; however Table 2 and the listing of adverse reactions occurring at a frequency of 1% or greater are not.
>
> Specifically, Table 12 in the 120-day safety update contains numerous adverse events possibly related to opioid use that are not included in Table 2 in the draft package insert. Also, the listing of AEs occurring in more than 1% of the study population should include all treatment-emergent adverse events, not just opioid related AEs.
>
> We recommend that you refer to the labels for existing transmucosal fentanyl products. If you are not able to submit tables and listings that provide the additional required information, we will create the tables and listings to be included in the product label.

Please let me know if you have any questions.

Thanks,
Kim

From: David T. Wright [mailto:DTWright@bdsinternational.com]
Sent: Wednesday, June 04, 2008 10:56 AM
To: Compton, Kimberly
Subject: BDSI Attendees on the Teleconference Yesterday

Kim:

Here is a list of the BDSI attendees on the teleconference yesterday.

Renee Boerner, PhD	Project Director, CMC Regulatory Compliance
Andrew Finn, PharmD	Executive Vice President, Product Development
Ken Schupp	Associate Director, Analytical Development / Quality Control
David Varley	Director, Manufacturing
Niraj Vasisht, PhD	Vice President, Pharmaceutical Development
David T Wright, PhD, RAC	Director, Regulatory Affairs

Please send a list of the Agency attendees when convenient.

As promised, we'll send a revised response as soon as possible. We look forward to further discussions next week.

Best regards, Dave

David T Wright, PhD, RAC
Director, Regulatory Affairs
BioDelivery Sciences International (BDSI)
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Raleigh, NC 27607

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/s/

Kimberly Compton
8/5/2008 06:54:18 PM
CSO

Compton, Kimberly

From: Compton, Kimberly
Sent: Friday, March 28, 2008 2:06 PM
To: 'David T. Wright'
Cc: Compton, Kimberly; Safarik, Michelle
Subject: BEMA website

Hello David,

We have reviewed the material that BDSI provided in response to our inquiry on the BEMA website and appreciate your quick response. The corrective actions you have taken appear acceptable for the most part; however, we request that you further amend the content to remove the following statement:

[redacted] b(4)

The terms "[redacted] and "[redacted]" are promotional and use of the phrase "[redacted]" b(4) makes it sound like the drug will be approved for more indications than the one currently sought, despite the inclusion of the full proposed indication later on.

Please let me know if you have any questions on this request.

Thanks,

Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
301-796-1191

From: David T. Wright [mailto:DTWright@bdsinternational.com]
Sent: Thursday, March 27, 2008 2:28 PM
To: Compton, Kimberly

Cc: Safarik, Michelle
Subject: RE: check out the BEMA website
Importance: High

Kim:

Please find attached an advanced copy of the cover letter and attachments, including a letter from Mark Sirgo our CEO and the response document (both clean and with tracked changes) for your information and convenience. This email will be followed by a submission of these documents via the gateway early next week.

Best regards, Dave

David T Wright, PhD, RAC
Director, Regulatory Affairs
BioDelivery Sciences International (BDSI)
801 Corporate Center Drive, Suite 210
Raleigh, NC 27607

T: 919.582.9050
F: 919.582.9051

From: Compton, Kimberly [mailto:kimberly.compton@fda.hhs.gov]
Sent: Thursday, March 20, 2008 11:01 AM
To: David T. Wright
Cc: Safarik, Michelle; Compton, Kimberly
Subject: FW: check out the BEMA website

Hi Dave,

Our team has noted the following on BDSI's BEMA website as of today, March 20, 2008:

BDSI's Current BEMA Products In Development

BEMA Fentanyl (Breakthrough Pain in Patients on Opioids)

There is a clear need for additional narcotic agents in alternative dosage forms to provide rapid pain relief.

BEMA Fentanyl is expected to meet the need for new narcotics and will be ideal for:

- breakthrough pain in opiod-tolerant patients
- post-operative patients following step-down from IV narcotics; hospitalized patients or outpatients without IV access
- emergency rooms patients where available IV lines are limited or impractical

We have the following questions in regard to this:

1. How long has this been posted on your website?

2. What are your plans for this website and will you be posting any corrective messages?

3. How will you assess the potential for off-label use this has created in the scheme of your RiskMAP?

4. What elements of your risk minimization program will provide corrective actions to ensure that the postoperative and emergency room uses will be understood as dangerous and potentially fatal?

5. How will you measure the success of these corrective actions?

6. Has the information presented on your website promoting postoperative and emergency room use been presented in any other program, materials, or meetings?

We have also shared this information and our request for response with our colleagues in DDMAC and they may contact you directly with additional follow-up.

We require a full response to these questions in no more than one week.

Thank you,
Kim

Kimberly Compton
Kimberly Compton, R.Ph.
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products (HFD-170)
301-796-1191

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/s/

Kimberly Compton
8/5/2008 06:52:39 PM
CSO