CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-723

Chemistry Review(s)

Team Leader Memo: CMC Evaluation of NDA Amendment dated August 25, 2004
NDAs 21446, 21723, 21724,
Ravi S. Harapanhalli, Ph.D.
August 31, 2004

The amendment dated August 25, 2004 was received by the EDR on August 30, 2004. The following is the review of the revised responses from Pfizer for the Agency questions discussed on June 8, 2004. In view of the findings in this review, the above NDAs are "approvable" from CMC perspective.

Agency Question 4f dated May 25, 2004:

Provide the following additional specifications for the carcinogenic impurity [ ] and the structural alert impurities in the drug substance:

[ ] NMT PPM
NMT PPM
NMT PPM
NMT PPM
[ ] NMT PPM

Pfizer's revised response following their original response dated May 25, 2004:

Response 4f:

We commit to test the drug substance for the above impurities to the specifications requested [ ] through the first 3 commercial batches made [ ], as follows.

[ ]

The need for a final drug substance specification for the above impurities will be assessed following review of the test results.

Alternatively we may choose to control [ ] We commit to proposing [ ] if applicable, following review of the test results.

Accordingly, we hereby provide a replacement page (Page 10) of the comparability protocol, which reflects the clarification made above. The replacement page is provided in **cmc\.**

Evaluation: Inadequate

Pfizer clarifies that [ ] will be limited to NMT PPM because of the fact that [ ] upon subsequent [ ]; may not necessarily be associated with [ ] as [ ] in the final drug substance,

rendering a specification for [ ] more appropriate than [ ] [ ] Adequate data or reasoning is not provided for this position. Although [ ] is likely to [ ] leading up to the drug substance, the prudent step would be to monitor [ ] It is not clear why Pfizer should not monitor [ ]

Pfizer has provided a replacement page (Page 10) of the comparability protocol with the above clarifications. Pfizer also states that [ ]. Pfizer commits to proposing [ ] specification for [ ] if applicable, following review of the test results.

Comment to Pfizer:

You provided a clarification to the comparability protocol [ ] of drug substance synthesis stating that [ ] would be limited to NMT — PPM instead [ ] Adequate justification was not provided for not monitoring [ ] in the drug substance.

Provide further, adequate justification for the lack of monitoring [ ] in the drug substance. As you are aware, [ ] a structural alert compound. In your recent amendment, you provided a clarification to the comparability protocol for [ ] would be limited to NMT — PPM, but there is no apparent monitoring [ ]

The following are Pfizer's revised responses to the FDA comments dated June 08, 2003 that were discussed during the teleconference on the same day.

FDA Comment 1

We remind you of your commitment in the Amendment dated 13-MAY-2004 to test the first three Ringaskiddy lots of pregabalin for [ ] has been implemented. If the observed levels are more than —PPM, submit the data in a prior-approval supplement and propose a specification of NMT [redacted] PPM for this impurity.

CMC Response 1

Once [ ] in Ringaskiddy we commit to test the first 3 commercial lots for [ ] If the observed levels are [redacted] ppm the data will be reported and a specification of NMT [redacted] ppm for this impurity will be established.

Evaluation: Adequate

Pfizer commits to monitoring [ ] at Ringaskiddy and to take an appropriate action as recommended.

FDA Comment 2

The batch reference [ ] was omitted for the manufacturing example in the NDA submission, Section 3.2.S.2.2.2 page 34. Adequately document the batch reference for the regulatory starting material in all future manufacturing campaigns.

CMC Response 2

The batch reference number(s) for the regulatory starting material is(are) documented and will be provided in all future correspondence with regard to this NDA, as appropriate.

Evaluation: Adequate

FDA Comment 3

The data in support of — retest interval for the drug substance were based on only three batches from Holland, MI. Statistical analysis revealed that at end of proposed retest interval, the tolerance limits were outside the acceptable range of [ ] Therefore, a retest interval of — is granted at this time. Accrual of additional stability data may qualify for a future extension of the retest interval.

CMC Response 3

Per the table below, we currently have — stability data available for Little Island drug substance lots on stability and — data available for Ringaskiddy lots on stability. (Attachments 1 and 2) All drug substance specifications were met. We expect to have — data available for Ringaskiddy later this year, which we will submit via annual report. Therefore, we would like to maintain the — drug substance retest interval.

Drug Substance Stability – Current Months Available for Ringaskiddy and Little Island

Lot #	Manufacturing Site	Date on Stability	Months of Stability Data Available
01198003	Ringaskiddy	10/2001	
01198004	Ringaskiddy	10/2001	
01198005	Ringaskiddy	10/2001	
003RP	Little Island	7/2000	
004	Little Island	7/2000	
005	Little Island	7/2000	
007	Little Island	8/2000	

Attachments 1 and 2 are provided in **cmc\substance**.

Evaluation: Inadequate

Pfizer submitted additional stability data for three drug substance made at Ringaskiddy, Ireland (— commercial scale) and four batches made at Little Island, Ireland (— pilot scale).

The Ringaskiddy data indicated that the — purity was not tested at — time point. Little Island data indicates that impurities and/or — purity were not determined at — time point. Additionally, information on the container closure system was

not provided in the amendment. These lapses in the new data and the concerns from Holland, MI site do not support a retest interval of [ ] at this time. However, as discussed in earlier communication with Pfizer, accrual of additional satisfactory real time data would be the basis for extending the retest interval to [ ] through the annual report.

Comment to Pfizer:

In support of a retest interval of [ ] for the drug substance, you provided additional stability data on three batches from Ringaskiddy and four batches from Little Island sites but did not provide information on the container closure systems. Similarly, testing of the impurities and — purity were not carried out at [ ] at Ringaskiddy site and at the end [ ] at Little Island site. In view of this and the previous assessment of the data from Holland, MI site, a retest interval of [ ] granted at this time. However, based on the accrual of additional satisfactory stability data, you may extend the retest period through the annual reporting mechanism.

FDA Comment 4

Provide a revision to the drug substance specifications with the acceptance criteria for the bulk — of NLT [ ] which is reflective of the batch experience by the proposed [ ] process. This may be submitted in the next annual report.

CMC Response 4

Provided below is a summary of — bulk — results from the most recent drug substance lots (including commercial scale) produced by [ ] in Little Island and Ringaskiddy, Cork, Ireland, respectively.

— Bulk — for API Lots Produced In Ireland

API Lot #	Site	Date of Manufacture	Batch Size (kg)	Bulk — (g/mL)[a]	Released and Shipped to:
03198015	Ringaskiddy	07-Nov-2003			
03198017	Ringaskiddy	13-Nov-2003			
03198019	Ringaskiddy	19-Nov-2003			
03198011	Ringaskiddy	22-Oct-2003			
03198016	Ringaskiddy	11-Nov-2003			
03198010	Ringaskiddy	22-Oct-2003			
03198012	Ringaskiddy	29-Oct-2003			
03198013	Ringaskiddy	29-Oct-2003			
03198014	Ringaskiddy	29-Oct-2003			
03198002	Ringaskiddy	14-Oct-2003			
03198005	Ringaskiddy	16-Oct-2003			

API Lot #	Site	Date of Manufacture	Batch Size (kg)	Bulk — (g/mL)[a]	Released and Shipped to:
03198021	Ringaskiddy	21-Nov-2003			
03198022	Ringaskiddy	21-Nov-2003			
03198006	Ringaskiddy	16-Oct 2003			
03198004	Ringaskiddy	16-Oct-2003			
03198007	Ringaskiddy	22-Oct-2003			
03198008	Ringaskiddy	22-Oct-2003			
03198003	Ringaskiddy	14-Oct-2003			
003RP	Little Island	30-Jun-00			
004	Little Island	30-Jun 00			
005	Little Island	30-Jun-00			
007	Little Island	02-Aug-00			
008	Little Island	23-Aug-01			
009	Little Island	23-Aug-01			
010	Little Island	23-Aug-01			
011	Little Island	23-Aug-01			
012	Little Island	23-Aug-01			
013	Little Island	23-Aug-01			
001AD	Little Island	24-May-02			
002AD	Little Island	24-May-02			

a = specification is NLT [redacted]

This recent batch experience supports our current specification of NLT [redacted]. We will obtain additional commercial scale drug substance batch experience and formulation experience with Ringaskiddy and Little Island lots to evaluate any change to the bulk — specification.

Evaluation: Inadequate

The manufacturing process [ ]]. The above data do not support the acceptance criteria of NLT — for the [ ]]. The lowest is —. The proposed limit for [ ] is not amenable to "mean ± 3 sigma" approach and should be supported by the actual data. [ ] is a critical process parameter that impacts on the [ ]

As agreed upon in a teleconference dated June 4, 2004, this issue will be resolved through the evaluation of additional data that will be submitted in the annual report.

FDA Comment 5-6

A — shelf life is granted only for the currently proposed configuration of the drug product, i.e. 60 cc HDPE bottles containing 60 capsules for the strengths 25-, 50-, 75-, and 100 mg.

For the strengths 150-, 200-, 225-, and 300 mg capsules, a shelf life of — is grantable at this time. Based on the accrual of additional real time stability data on the appropriate container/closer configurations, the shelf life may be extended in the next annual report.

CMC Response 5-6
Stability data provided in Section 3.2.P.8.3.1, Stability Data Tables supports a [ ] shelf-life for all strengths. Stability acceptance criteria for appearance, assay, degradation and impurities, and dissolution tests were met at [ ] (3 studies), [ ] (8 studies) as well as for the [ ] studies ranging from [ ]. Demonstrated stability was independent of packaging material (bottle ~~vs blister~~) or configuration. Data provided in the original NDA for 100 count HDPE bottles adequately justifies packaging in the new 60-count HDPE (blue ~ bottles. An agreement was reached between FDA and Pfizer in a August 3, 2001 memo from Nancy Sager to Mr. Victor Clavelli whereby legacy Parke-Davis products could be switched to new HDPE (blue ~ bottles without additional stability work in the new bottle (Attachment 3). Furthermore, in response to two queries from S. Kelly, we provided [ ] analysis data for the 2 bottle types over the range of bottle sizes for the specific capsule size and count for each capsule strength (25 mg to 300 mg) to demonstrate that the new bottle provides equivalent protection. We request to maintain [ ] shelf life for all strengths.

Attachment 3 is provided in **cmc\product**.

Evaluation: Inadequate

The above reasoning was also provided during the teleconference and was discussed in detail. The Agency stated that based on the data on bracketing of packaging configurations with acceptable barrier properties and head space analysis, it was concluded that only [ ] stability data was relevant for the higher strengths, 150-, 200-, 225-, and 300-mg capsules. Additionally, the ICH Q3E principles were applied in extending the expiration dating to 12 more months. This led to a grantable expiration dating of [ ] Therefore, we do not agree with Pfizer's position to retain the expiration dating of [ ] at this time. Accrual of additional real time data may support the extension to [ ] through annual report mechanism.

Comment to Pfizer:

Either revise your proposed shelf life of the 150-, 200-, 225-, and 300-mg capsules to conform to the data provided in the NDA which we believe supports — or provide further data and justification to better support your proposed — shelf-life.

FDA Comment 7
Revise the post-approval stability protocol to include semi-annual testing in the first and second year of testing.

CMC Response 7
The post-approval stability protocol has been revised to include time points of — and — (Attachment 4).

Attachment 4 is provided in **cmc\product**.

Evaluation: Adequate

Postapproval Stability Protocol for Annual Commercial Lots

Storage Condition	Interval (Month)
	[
25°C/60%RH	]

Tests to be applied in accordance with the above protocol include:

[ ]

FDA Comment 8

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, your continued cooperation is expected to resolve any problems that may be identified.

CMC Response 8

Pfizer will cooperate fully regarding any future queries regarding methods validation.

Evaluation: Adequate

Pfizer's NDAs: 21446, 21723, 21724, CMC Comments to the letter

In your amendment dated May 31, 2004 you provided the following additional CMC information in support of your revisions to your earlier responses dated June 08, 2004.

1. Provide further, adequate justification for the lack of monitoring of — along with its precursor in the drug substance. As you are aware, — is a structural alert compound. In your recent amendment, you provided a clarification to the comparability protocol for the change in the route of drug substance synthesis stating that — the precursor of — would be limited to NMT — PPM, but there is no apparent monitoring or limits placed for — itself.
2. Provide information on the container closure systems used to generate the additional stability data on three batches from Ringaskiddy and four batches from Little Island sites you provided in support of a retest interval of — for the drug substance.
3. Either revise your proposed shelf life of the 150-, 200-, 225-, and 300-mg capsules to conform to the data provided in the NDA which we believe supports —, or provide further data and justification to better support your proposed — shelf-life.

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/s/

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8/31/04 01:40:39 PM
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