CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-272

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI (HFD-705)

NDA NO.:	22-272
SERIAL NO.:	S_000
DATE RECEIVED BY THE CENTER:	May 13, 2008, June 15, 2009
DRUG NAME:	Oxycodone HCL 10, 15, 20, 30, 40, 60, and 80 mg TR
DOSAGE FORM:	Tablets
INDICATION:	Pain management
SPONSOR:	Purdue Pharma, L.P.
DOCUMENTS REVIEWED:	Electronic Copy Dated May 13, 2008, June 15, 2009
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D. (HFD-705)
NAME OF CHEMISTRY REVIEWER:	Craig M. Bertha, Ph.D.

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Meiyu Shen, Mathematical Statistician

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Distribution: NDA 22-272
HFD-705/Y. Tsong, Ph.D.
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EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The sponsor submitted a 24-month stability studies for (b) (4) 100, (b) (4) count bottles of Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months on May 13, 2009. The sponsor also submitted a 24-month stability studies for (b) (4) count bottles for the 60 mg and 80 mg TR Tablets with the request for an extrapolated shelf life of 24 months on June 15, 2009. (b) (4) .

The original and revised dissolution specification limits for Oxycodone HCL 10, 15, 20, 30, 40, 60, and 80 are listed in the Table 1.

Product	Dissolution Time	Specification		
		Original	12-month update	24-month update
10, 15, and 20 mg	1st hour	(b) (4)		
	4th hour			
	12th hour	NLT (b) (4)	NLT (b) (4)	NLT (b) (4)
30 and 40 mg	1st hour	(b) (4)		
	4th hour			
	12th hour	NLT (b) (4)	NLT (b) (4)	NLT (b) (4)
60 mg	1st hour			(b) (4)
	4th hour			
	12th hour			NLT (b) (4)
80 mg	1st hour			(b) (4)
	4th hour			
	12th hour			NLT (b) (4)

When the revised specification is used, based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through 24 months for 10, 15, 20, 30, 40, 60, and 80 mg TR tablets. The analysis showed that 24-month expiration was established for 10, 15, 20, 30, 40, 60, and 80 mg TR tablets. However, because there is no data for 60 and 80 mg with 100 counts per package, the shelf-life for 60 and 80 mg with 100 counts per package are not established.

1.2 Overview of the Submission

The sponsor submitted a 24-month stability studies for (b) (4), 100, (b) (4) count bottles of Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months on May 13, 2009. The sponsor also submitted a 24-month stability studies for (b) (4) count bottles for the 60 mg and 80 mg TR Tablets with the request for an extrapolated shelf life

of 24 months on June 15, 2009. One batch per strength was used in stability studies. Each batch was split into (b) (4) package counts, such as (b) (4), 100, (b) (4) counts per package.

The statistical analyses were not performed for the assay data or the dissolution data at 1 hour, 4 hours, or 12 hours of Oxycodone. The statistical analyses were not performed for degradation data because nearly all of the reported values except a few observations were reported as NMT (b) (4)

1.3 Principal Findings

1.3.1 Sponsor's Results and Conclusions

(I) Stability analysis for Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets

In the submission on May 13, 2009, the sponsor tabulated long term stability data up to 24 months for Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets. The sponsor's conclusions were based on the eye-balling the results and specifications:

1. Assay of Oxycodone HCl: all assay results were within the current proposed specification (b) (4) label claim) for the long-term 24-month stability data.

2. Degradation products:
(b) (4): observed values were <0.1%.
2) Individual unknown degradation product
All individual unknown degradation products were within the specification limit of NMT (b) (4).
From samples at all testing intervals, there were only four cases where the unknown degradation products were observed in levels at or above (b) (4) as listed below:
(b) (4) in 20 mg, 100 count at 1 month room temperature
in 40 mg, 100 count at 1 month room temperature
in 30 mg, (b) (4) count at 12 months room temperature
in 10 mg, (b) (4) count at 24 months room temperature
To provide additional information of the unknown in the 30 mg stability sample and to confirm the original data of (b) (4) for this unknown, two additional sample solutions of the 30 mg, (b) (4) count, 12 months, room temperature stability sample were prepared and analyzed. This unknown in the two retested samples were below the LOD limit of 0.05%.

3). Total degradation Products
The results at all testing intervals (through 24 months at long-term stability) were within the specification (NMT (b) (4)) and the values ranged from NMT (b) (4)

From samples at all testing intervals, there was only one case where the total degradation products was observed at a level above (b) (4) The total degradation products result was (b) (4) in the 30 mg, (b) (4) count, 12 months room temperature stability sample.

4). Dissolution
All dissolution results from long-term stability data through 24 months met the proposed specifications in Table 1.

(b) (4)

(II) Stability analysis for Oxycodone HCL 60 and 80 mg TR Tablets

In the submission on June 15, 2009, the sponsor tabulated long term stability data up to 24 months for Oxycodone HCL 60 and 80 mg TR Tablets. The sponsor's conclusions were based on the eye-balling the results and specifications:

1. Assay

All assay results are within the current proposed specification (b) (4) label claim) for the long-term stability samples tested through 24 months.

2. Degradation Products

1) Known Degradation Product: (b) (4)

All (b) (4) results from long-term stability data (through 24 months in (b) (4) count bottles) were within the current proposed specification limit of NMT (b) (4), and all values were (b) (4)

2) Individual Unknown Degradation Product

From all long-term stability data (through 24 months in (b) (4) count bottles), there was only one incidence where unknown degradation products were observed in levels at or above (b) (4); two unknowns in amounts of (b) (4) were observed in the 60 mg initial sample. It should be noted that these two unknowns were not seen in the later stability samples of the same batch.

Except for these two unknowns in the 60 mg initial sample; all unknowns, if observed, were (b) (4) All individual unknown degradation products were within the proposed specification limit of NMT (b) (4).

3) Total degradation Products

The total degradation products at all testing intervals (through 24 months long-term stability) were within the proposed specification (NMT (b) (4)) and the values ranged from < LOQ (0.10%) to (b) (4). From samples at all storage conditions and test intervals, except for the 60 mg initial sample where the total degradation products was (b) (4) all values were (b) (4)

4) Dissolution

All dissolution results from long-term stability data (through 24 months in (b) (4) count bottles), met the current proposed specifications in Table 1.

The sponsor asked the proposed shelf-life of 24 months for all (b) (4) package (b) (4)

1.3.2 Reviewers' Results and Conclusions

The reviewer performed the standard Office of Biostatistics (OB) stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. In this fashion one can determine whether the data are internally consistent (with pooled slopes and pooled

intercepts) and whether each product characteristic supports an extrapolated shelf life of 24 months. Based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through 24 months when the revised specification is used.

1.3.3 Statistical Issues

The sponsor eye-ball method for comparing the results and specification was not accepted.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

The sponsor submitted a 24-month stability studies for (b) (4), 100, (b) (4) count bottles of Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months on May 13, 2009. The sponsor also submitted a 24-month stability studies for (b) (4) count bottles for the 60 mg and 80 mg TR Tablets with the request for an extrapolated shelf life of 24 months on June 15, 2009. One batch per strength was used in stability studies. Each batch was split into (b) (4) package counts, such as (b) (4) 100, (b) (4) counts per package.

The statistical analyses were not performed for the assay data or the dissolution data at 1 hour, 4 hours, or 12 hours of Oxycodone. The statistical analyses were not performed for degradation data because nearly all of the reported values except a few observations were reported as NMT (b) (4).

2.2 Overview of the Stability Program and Studies Reviewed

The assay data of Oxycodone, the assay data of degradation products ((b) (4), unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone were submitted under 25^0C/60% RH condition in SAS transport format.

The statistical analyses were performed for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. However, the statistical analyses were not performed for degradation data because nearly all of reported values except a few observations were below LOQ level (0.1%).

2.3 Data Analyzed and Sources

The sponsor submitted the data in electronic format on May 13 and June 15, 2009. The data are located in the EDR at the following link: \\cdsesub1\n22272\S_00.

2.4 Stability Study

2.4.1 Data

The assay data of Oxycodone, the assay data of degradation products (b) (4), unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone were submitted under 25^0C/60% RH condition in SAS transport format.

2.4.2 Sponsor's Analysis, Results and Conclusions

In the submission on May 13, 2009, the sponsor tabulated long term stability data up to 24 months for Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets.

In the submission on June 15, 2009, the sponsor tabulated long term stability data up to 24 months for Oxycodone HCL 60 and 80 mg TR Tablets.

In both submissions, the sponsor's conclusions were based on the eye-balling the results and specifications.

The sponsor's conclusions are listed below:

1. The sponsor concluded the 24-month shelf-life was supported for all Oxycodone HCl 10, 15, 20, 30 and 40 mg TR tablets can be supported.

(b) (4)

2.4.3 Reviewers' Analysis, Results and Conclusions

The reviewer performed the standard Office of Biostatistics (OB) stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. In this fashion one can determine whether the data are internally consistent (pooled slopes and pooled intercepts) and whether each product characteristic supports an extrapolated shelf life of 24 months. In the analysis, the initial value was repeatedly added to each of (b) (4) packages. Data was deleted when package=0. This is one of alternative approaches favor to the sponsor because it assumes the same initial value for each package when package variability is ignored.

The analysis results are listed in Table 2. The specifications in Table 1 are used according to the sponsor's updates. Based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through 24 months. The analysis showed that 24-month expiration was established for 60 and 80 mg with (b) (4) counts per package. However, because there is no data for 60 and 80 mg with 100 counts per package, the shelf-life for 60 and 80 mg with 100 counts per package are not established.

Table 2: Analysis of Oxycodone HCL assay and its dissolution up to 24 months stability data for 10, 15, 20, 30, 40, 60, and 80 mg TR tablets using the revised specification

Strength	Parameter	Final model	Estimated shelf	Estimated shelf h
10 mg	Dissolution at 1 hr	(b) (4)		
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
15 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
20 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
30 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
40 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
60 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
80 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			

2.5 Statistical and Technical Issues

The sponsor's conclusions were based on the eye-balling the results and specifications.

2.6 Statistical Evaluation of Collective Evidence

The reviewer performed the independent stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. Based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through 24 months for 10, 15, 20, 30, 40, 60, and 80 mg TR tablets when the revised specification is used. However, because there is no data for 60 and 80 mg with 100 counts per package, the shelf-life for 60 and 80 mg with 100 counts per package are not established.

2.7 Conclusions and Recommendation

Based on this reviewer's analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through 24 months when the revised specification is used.

The sponsor's request for 24 month shelf life is established for 10, 15, 20, 30, 40, 60, and 80 mg TR tablets. However, because there is no data for 60 and 80 mg with 100 counts per package, the shelf-life for 60 and 80 mg with 100 counts per package are not established.

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STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI (HFD-705)

NDA NO.:	22-272
SERIAL NO.:	S_000
DATE RECEIVED BY THE CENTER:	Dec. 18, 2007, April 23, 2008
DRUG NAME:	Oxycodone HCL 10, 15, 20, 30, and 40 mg TR
DOSAGE FORM:	Tablets
INDICATION:	Pain management
SPONSOR:	Purdue Pharma, L.P.
DOCUMENTS REVIEWED:	Electronic Copy Dated Dec. 18, 2007, April 23, 2008
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D. (HFD-705)
NAME OF CHEMISTRY REVIEWER:	Craig M. Bertha, Ph.D.

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EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The sponsor submitted a 9 months stability studies for three package counts of Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months on Dec.18, 2007, updated the submission for the stability studies of 100 counts per package with 12 months data on Feb 15, 2008, and tightened the 4 hour dissolution criteria on March 13, 2008. The sponsor updated the submission for the stability studies of (b) (4) 100, (b) (4) counts per package with 12 months data on April 23, 2008 and revised the 4 hour dissolution criteria from (b) (4) to (b) (4) for the 10, 15, and 20 mg strengths and (b) (4) to (b) (4) for the 30 and 40 mg strengths. One batch per strength was used in stability studies. Each batch was split into (b) (4) package counts, such as (b) (4), 100, (b) (4) counts per package. When the revised specification is used, based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through (b) (4) months. The analysis showed that 24-month expiration was established.

1.2 Overview of the Submission

In the original submission, the sponsor provided 9 months drug product stability data for three package counts of Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months on Dec.18, 2007, updated the submission for the stability studies of 100 counts per package with 12 months data on Feb 15, 2008, and tightened the 4 hour dissolution criteria on March 13, 2008. One batch per strength was used in stability studies. Each batch was split into (b) (4) package counts, such as (b) (4), 100, (b) (4) counts per package. The sponsor updated the submission for the stability studies of (b) (4), 100, (b) (4) counts per package with 12 months data on April 23, 2008 and revised the 4 hour dissolution criteria from (b) (4) to (b) (4) for the 10, 15, and 20 mg strengths and (b) (4) to (b) (4) for the 30 and 40 mg strengths.

The statistical analyses were performed for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. However, the statistical analyses were not performed for degradation data because nearly all of the reported values except a few observations were below LOQ level (0.1%).

1.3 Principal Findings

1.3.1 Sponsor's Results and Conclusions

In the submission, the sponsor included the analysis of long term stability data up to 12 months for Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets conducted by (b) (4) The sponsor's conclusions are listed below:

1. Assay of Oxycodone HCl: The shortest calculated shelf-life for the long term condition was (b) (4) months for the 30 mg tablet strength from the analysis of the long-term stability data.

2. Dissolution: The sponsor revised specification limits for the stability sample in the submission dated on April 23, 2008 as shown in Tables 1 were recommended. When the long term stability data were analyzed against the new specification limit, all calculated shelf lives were longer than the proposed 24-month shelf life, except for the 4-hour dissolution of the 40 mg strength, equal to 24 months.

Table 1: Original and Revised Dissolution Specification Limits for Oxycodone HCl

Original Specification Limit: 10, 15, 20, 30, 40 mg TR Tablets	Revised Specification Limit: 10, 15 and 20 mg TR Tablet	Revised Specification Limit: 30 and 40 mg TR Tablet
1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)	1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)	1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)

1.3.2 Reviewers' Results and Conclusions

The reviewer performed the standard Office of Biostatistics (OB) stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. In this fashion one can determine whether the data are internally consistent (with pooled slopes and pooled intercepts) and whether each product characteristic supports an extrapolated shelf life of 24 months. Based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through 24 months when the revised specification is used.

1.3.3 Statistical Issues

The sponsor's approach was not accepted for the following reasons.

1) Poolability test for package slope

(b) (4) used the following strategy to test the poolability of slopes across packages at the 0.05 level of significance.

Let us define y be the response variable, such as assay, or dissolution, and β_0 be the intercept, β_i be slope for the i^{th} package (the 1^{st} package is 0 counts per package, the 2^{nd} package is (b) (4) counts per package, and the 3^{rd} package is 100 counts per package, the 4^{th} package is (b) (4) counts per package). The model is $y= \beta_0+ (\beta+\beta_i)*Time$, i=1, 2, 3, 4. (b) (4) proposed to test

H_0: $\beta_1 = \beta_2= \beta_3 = \beta_4=\beta$, reduced model (or pooling slopes)
H_a: $\beta_{i\neq} \beta_{j,}$ $i\neq j$, full model

The SAS codes used are:

```
Proc glm;
Class package;          *package has 4 levels: 0, (b) (4), 100, (b) (4) counts per package;
Model y=time    Package*time;
Run;
```

If the p-value for term package*time in the full model was < 0.05, the NULL is rejected and OSC concluded that each package had a separate slope. Otherwise, they concluded that all package had the common slope.

This statistical strategy is different from the OB standard poolability testing.

2). The fact that the sponsor used the same initial observation as 0 package type is not acceptable because there is only one observation for 0 package type. Hence initial value of (b) (4) package types are treated as missing in the model and pooling slope is not really about pooling the slopes after initial of the three batches.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

The sponsor provided 9 months drug product stability data for (b) (4) package counts of Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months on Dec.18, 2007, updated the submission for the stability studies of 100 counts per package with 12 months data on Feb 15, 2008, and tightened the 4 hour dissolution criteria on March 13, 2008. The sponsor updated the submission for the stability studies of (b) (4), 100, (b) (4) counts per package with 12 months data on April 23, 2008 and revised the 4 hour dissolution criteria from (b) (4) to (b) (4) for the 10, 15, and 20 mg strengths and (b) (4) to (b) (4) for the 30 and 40 mg strengths. One batch per strength was used in stability studies. Each batch was split into (b) (4) package counts, such as (b) (4) 100, (b) (4) counts per package. In addition, data through 6 months storage at the 40^0C/75% RH were also submitted.

2.2 Overview of the Stability Program and Studies Reviewed

The assay data of Oxycodone, the assay data of degradation products (b) (4), unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone were submitted under 25^0C/60% RH condition in SAS transport format. The assay data of Oxycodone, the assay data of degradation products (b) (4), unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone were submitted under 40^0C/75% RH in pdf format.

The statistical analyses were performed for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. However, the statistical analyses were not performed for degradation data because nearly all of reported values except a few observations were below LOQ level (0.1%).

2.3 Data Analyzed and Sources

The sponsor submitted the data in electronic format on December 18, 2007. The data are located in the EDR at the following link: \\cdsesub1\n22272\S_00.

2.4 Stability Study

2.4.1 Data

The assay data of Oxycodone, the assay data of degradation products ((b) (4) unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone were submitted under 25^0C/60% RH condition in SAS transport format.

2.4.2 Sponsor's Analysis, Results and Conclusions

In the submission, the sponsor included the analysis of long term stability data up to 12 months for Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets conducted by (b) (4) analysis result is listed in Table 2.

Table 2 Estimated Shelf life from (b) (4)

Strength	Calculated Shelf-Life (Month)				
	Assay	Dissolution at 1 hr	Dissolution at 4 hr	Dissolution at 12 hr	Minimum of all shelf lives
10 mg	(b) (4)				
15 mg					
20 mg					
30 mg					
40 mg					

The sponsor's conclusions are listed below:

1. Assay of Oxycodone HCl: The shortest calculated shelf-life for the long term condition was 40 months for the 30 mg tablet strength from the analysis of the long-term stability data.

2. Dissolution: The sponsor revised the specification limits for the stability samples as shown in Table 1 were recommended. When the long term stability data were analyzed against the new specification limit, all calculated shelf lives were longer than the proposed 24-month shelf life, except for the 4-hour dissolution of the 40 mg strength, equal to 24 months.

2.4.3 Reviewers' Analysis, Results and Conclusions

The reviewer performed the standard Office of Biostatistics (OB) stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. In this fashion one can determine whether the data are internally consistent (pooled slopes and pooled intercepts) and whether each product characteristic supports an extrapolated shelf life of 24 months. In the analysis, the initial value was repeatedly added to each of three packages. Data was deleted when package=0. This is one of alternative approaches favor to the sponsor because it assumes the same initial value for each package when package variability is ignored.

The analysis results are listed in Table 4. The specifications in Table 3 are used according to the sponsor's updates. Based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through (b) (4) months. The analysis showed that 24-month expiration was established.

Table 3: Original and Revised Dissolution Specification Limits for Oxycodone HCl

Original Specification Limit: 10, 15, 20, 30, 40 mg TR Tablets	Revised Specification Limit: 10, 15 and 20 mg TR Tablet	Revised Specification Limit: 30 and 40 mg TR Tablet
1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)	1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)	1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)

Table 4: Analysis of Oxycodone HCL assay and its dissolution up to 12 months stability data for 10, 15, 20, 30, 40 mg TR tablets using the revised specification

Strength	Parameter	Final model	Estimated shelf life, month	Estimated shelf life, month
10 mg	Dissolution at 1 hr	(b) (4)		
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
15 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
20 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
30 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
40 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			

2.5 Statistical and Technical Issues

1). The sponsor's approach for poolability test for package slope was not acceptable.

2). The fact that the sponsor used the initial observation as 0 package type is not acceptable because there is only one observation for 0 package type.

2.6 Statistical Evaluation of Collective Evidence

The reviewer performed the independent stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. Based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through 24 months when the revised specification is used.

2.7 Conclusions and Recommendation

Based on this reviewer's analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through 24 months when the revised specification is used.

The sponsor's request for 24 month shelf life is established.

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STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI (HFD-705)

NDA NO.:	22-272
SERIAL NO.:	S_000
DATE RECEIVED BY THE CENTER:	Dec. 18, 2007
DRUG NAME:	Oxycodone HCL 10, 15, 20, 30, and 40 mg TR
DOSAGE FORM:	Tablets
INDICATION:	Pain management
SPONSOR:	Purdue Pharma, L.P.
DOCUMENTS REVIEWED:	Electronic Copy Dated Dec. 18, 2007
NAME OF STATISTICAL REVIEWER:	Meiyu Shen, Ph.D. (HFD-705)
NAME OF CHEMISTRY REVIEWER:	Craig M. Bertha, Ph.D.

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EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The sponsor submitted 9 month stability studies for three package counts of Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months on Dec.18, 2007. They updated the submission for the 100 count package with 12 month data on Feb 15, 2008, and tightened the 4 hour dissolution criteria on March 13, 2008. One batch per strength was used in stability studies. (b) (4) When the revised specification is used, the statistical analysis of the Oxycodone dissolution data at 1 hour and 4 hours did not support the request. The estimated extrapolated shelf-life for Oxycodone dissolution at 1 hour for 30 mg TR tablets is (b) (4) months. The estimated extrapolated shelf-life for Oxycodone dissolution at 4 hours for 40 mg TR tablets is (b) (4) months.

The sponsor provided 12-month stability data for only the 100 count package. (b) (4) Based on the ICH Q1E, the shelf-life can be extended up to 2* X (where X is the length of available data), but not exceeding X+ 12 months, or if refrigerated up to 2*X, but not exceeding X+6, if long-term data is amendable to statistical analysis and statistical analysis is performed,

1) For 100 counts per package, the shelf-life is (b) (4) months;
2) (b) (4)
3) If the product needs to be refrigerated (I could not confirm this), the shelf life is (b) (4) months for the 100 count package (b) (4)

The sponsor's request for a 24 month shelf life is not established.

1.2 Overview of the Submission

In this submission, the sponsor provided on Dec.18, 2007, 9 month drug product stability data in (b) (4) package counts for Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months. They updated the submission for the 100 counts per package with 12 month data on Feb 15, 2008, and tightened the 4 hour dissolution criteria on March 13, 2008. One batch per strength was used in the stability studies. Each batch was split into (b) (4) package counts, namely (b) (4) 100, (b) (4) counts per package. All long-term stability data were collected under the 25^0C/60% RH condition. In addition, data through 6 months storage at the 40^0C/75% RH were also submitted.

The assay data of Oxycodone, the assay data of degradation products (b) (4) unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone obtained under the 25^0C/60% RH condition were submitted in SAS transport format. The assay data of Oxycodone, the assay data of degradation products (b) (4) unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone obtained under 40^0C/75% RH were submitted in pdf format.

The statistical analyses were performed for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone when stored under the 25^0C/60% RH condition. Statistical analyses were not performed for degradation data because nearly all of the reported values were below LOQ level (0.1%).

1.3 Principal Findings

1.3.1 Sponsor's Results and Conclusions

In the submission, the sponsor included the analysis of long term stability data up to 12 months for Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets conducted by (b) (4) The sponsor's conclusions are listed below:

1. Assay of Oxycodone HCl: The shortest calculated shelf-life for the long term condition was (b) (4) months for the 30 mg tablet strength from the analysis of the long-term stability data.
2. Degradation Products:
   - (b) (4): Since (b) (4) data were below the reportable limit of 0.1% in most cases, no trend analysis was performed on (b) (4).
   - Individual unknown degradation products: There were no consistent increasing patterns observed in any of the data. Therefore, no trend analysis was conducted.
   - Total degradation products: The slopes were significantly different from zero only for the 10 mg and 15 mg strengths under accelerated storage conditions. However, the upper 95% confidence limits at 6 months accelerated of all strengths were below the current specification limits of (b) (4)%. Statistical analysis on the long-term stability (9 months of (b) (4) and (b) (4) counts, and 12 months of 100 count bottles) could not be performed since the levels of both the known (b) (4) and unknown degradation products were very low (within LOQ level of 0.1%).

3. Dissolution: Based on the statistical analysis of the 6-month accelerated data, new sets of specification limits for the stability sample were recommended as shown in Table 1. When the long term stability data were analyzed against the new specification limit, all calculated shelf lives were longer than the proposed 24-month shelf life, except for the 4-hour dissolution of the 40 mg strength.

Table 1: Original and filed Dissolution Specification Limits for Oxycodone HCl

Original Specification Limit: 10, 15, 20, 30, 40 mg TR Tablets	Filed Specification Limit: 10, 15 and 20 mg TR Tablet	Filed Specification Limit: 30 and 40 mg TR Tablet
1st Hour: (b) (4) 4th Hour: (b) (4) 12th Hour: NLT	1st Hour: (b) (4) 4th Hour: (b) (4) 12th Hour: NLT	1st Hour: (b) (4) 4th Hour: (b) (4) 12th Hour: NLT

1.3.2 Reviewers' Results and Conclusions

The reviewer performed the standard Office of Biostatistics (OB) stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. In this fashion one can determine whether the data are internally consistent (with pooled slopes and pooled intercepts) and whether each product characteristic supports an extrapolated shelf life of 24 months. Based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through (b) (4) months when the revised specification is used.

1.3.3 Statistical Issues

The sponsor's approach was not accepted for the following reasons.

1) Poolability test for package slope

(b) (4) used the following strategy to test the poolability of slopes across packages at the 0.05 level of significance.

Let us define y be the response variable, such as assay, or dissolution, and β_0 be the intercept, β be slope for the i^{th} package (the 1^{st} package reflect the release data before packaging, the (b) (4) package is (b) (4) counts per package, and the (b) (4) package is 100 counts per package, the 4^{th} package is (b) (4) counts per package). The model is $y= \beta_0+ (\beta+\beta_i)*Time$, i=1, 2, 3, 4. (b) (4) proposed to test

H_0: $\beta_1 = \beta_2= \beta_3 = \beta_4=\beta$, reduced model (or pooling slopes)
H_a: $\beta_{i\neq} \beta_{j,}$ $i\neq j$, full model

The SAS codes used are:

```
Proc glm;
Class package;          [package has 4 levels: 0, (b) (4) 100, (b) (4) counts per package;]
Model y=time    Package*time;
Run;
```

If the term package*time in the full model has a p-value < 0.05, the NULL is rejected and they concluded that each package has a separate slope. Otherwise, they concluded that all packages have a common slope.

This statistical strategy is different from the OB standard poolability testing.
2). The fact that the sponsor used the release observations as 0 package type is not acceptable. In the pooling test for slopes, there is only one observation for 0 package type and no release data used for (b) (4), 100, (b) (4) counts per package. If the slopes can be pooled, the release data is used in the regression line. If the slopes cannot be pooled, the release data is ignored in estimation of shelf-life.

3). The shortest estimated shelf from (b) (4), listed in Table 2, is (b) (4), not 24 months. Hence the 24-month shelf life is not established.

4). The sponsor provided 12-month stability data only for 100 counts per package. The other (b) (4) packages have data for only 9 months. Based on the ICH Q1E, the shelf-life is up to 2* X (where X is length of time for the available data), but not exceeding X+ 12 months, or if refrigerated up to 2*X, but not exceeding X+6 months, if long-term data is amendable to statistical analysis and statistical analysis is performed,
a) For 100 counts per package, the shelf-life is (b) (4) months;
b) (b) (4)
c) If the product needs to be refrigerated (I could not confirm this), the shelf life is (b) (4) months for the 100 count package (b) (4).

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

In this submission, the sponsor provided 9 months drug product stability data for three package counts of Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets with the request for an extrapolated shelf life of 24 months on Dec.18, 2007, updated the submission with 12 months data for the stability studies of 100 counts per package on Feb 15, 2008, and tightened the 4 hour dissolution criteria on March 13, 2008. One batch per strength was used in the stability studies. Each batch was split into (b) (4) packages, namely (b) (4) 100, (b) (4) count bottles. All long term stability data were collected under the 25^0C/60% RH condition. In addition, data through 6 months storage at the 40^0C/75% RH condition were also submitted.

2.2 Overview of the Stability Program and Studies Reviewed

The assay data of Oxycodone, the assay data of degradation products (b) (4) unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone collected under the 25^0C/60% RH condition were submitted in SAS transport format. The corresponding data collected under the 40^0C/75% RH were submitted in pdf format.

The statistical analyses were performed for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. The statistical analyses were not performed for degradation data because nearly all of reported values except a few observations were below the LOQ level (0.1%).

2.3 Data Analyzed and Sources

The sponsor submitted the data in electronic format on December 18, 2007. The data are located in the EDR at the following link: \\cdsesub1\n22272\S_00.

2.4 Stability Study

2.4.1 Data

The assay data of Oxycodone, the assay data of degradation products (b) (4) unknown degradation, and total degradation), the dissolution data at 1 hour, 4 hours, and 12 hours for Oxycodone collected under the 25^0C/60% RH condition were submitted in SAS transport format. The corresponding data collected under the 40^0C/75% RH were submitted in pdf format.

2.4.2 Sponsor's Analysis, Results and Conclusions

In the submission, the sponsor included the analysis of long term stability data up to 12 months for Oxycodone HCL 10, 15, 20, 30 and 40 mg TR Tablets conducted by (b) (4) . The (b) (4) analysis results are listed in Table 2.

Table 2 Estimated Shelf life from (b) (4)

Strength	Calculated Shelf-Life (Month)				
	Assay	Dissolution at 1 hr	Dissolution at 4 hr	Dissolution at 12 hr	Minimum of all shelf lives
10 mg	(b) (4)				
15 mg					
20 mg					
30 mg					
40 mg					

The sponsor's conclusions are listed below:

1. Assay of Oxycodone HCl: The shortest calculated shelf-life for the long term condition was (b) (4) months for the 30 mg tablet strength from the analysis of the long-term stability data.
2. Degradation Products:
   - (b) (4): Since (b) (4) data were below the reportable limit of 0.1% in most cases, no trend analysis was performed on (b) (4).
   - Individual unknown degradation products: There were no consistent increasing patterns observed in any of the data. Therefore, no trend analysis was conducted.
   - Total degradation products: The slopes were significantly different from zero only for the 10 mg and 15 mg strengths under accelerated storage conditions. However, the upper 95% confidence limits at 6 months accelerated of all strengths were below the current specification limits of 1.0%. Statistical analysis on the long-term stability (9 months of (b) (4) and (b) (4) counts, and 12 months of 100 count bottles) could not be performed since the levels of both the known (b) (4)) and unknown degradation products were very low (within LOQ level of 0.1%).

3. Dissolution: Based on the statistical analysis of the 6-month accelerated data, new sets of specification limits for the stability sample as shown in Table 1 were recommended. When the long term stability data were analyzed against the new specification limit, all calculated shelf lives were longer than the proposed 24-month shelf life, except for the 4-hour dissolution of the 40 mg strength.

2.4.3 Reviewers' Analysis, Results and Conclusions

The reviewer performed the standard Office of Biostatistics (OB) stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of each strength of Oxycodone. In

this fashion one can determine whether the data are internally consistent (pooled slopes and pooled intercepts) and whether each product characteristic supports an extrapolated shelf life of 24 months. In the analysis, the initial value was repeatedly added to each of (b) (4) packages. The designation 'package=0' was deleted. This is one of alternative approaches favor to the sponsor because it assumes the same initial value for each package when package variability is ignored.

The specifications in Table 3 are used according to the sponsor's updates. The analysis results are listed in Table 4. Based on these analyses and evaluations of the Oxycodone data, the product is expected to remain within specifications through (b) (4) months. The shelf life of mean dissolution at 1 hour for 30 mg TR tablets with (b) (4) counts per package was displayed in Figure 1. The shelf life of mean dissolution at 1 hour for 30 mg TR tablets with (b) (4) counts per package was displayed in Figure 2. The shelf life of mean dissolution at 4 hour for 40 mg TR tablets was displayed in Figure 3. The analysis showed that 24-month expiration was not established.

Table 3: Original and Revised Dissolution Specification Limits for Oxycodone HCl

Original Specification Limit: 10, 15, 20, 30, 40 mg TR Tablets	Revised Specification Limit: 10, 15 and 20 mg TR Tablet	Revised Specification Limit: 30 and 40 mg TR Tablet
1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)	1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)	1st Hour: (b) (4) 4th Hour: 12th Hour: NLT (b) (4)

The sponsor increased the lower limit for 12 hour dissolution data from (b) (4) to (b) (4). Hence the estimated shelf life for 12 hour dissolution using (b) (4) as the lower limit should be longer than that using (b) (4) as the lower limit. The sponsor tightened the specification limits for 4 hour dissolution as shown in Table 3. The sponsor did not change the specifications for 1 hour dissolution and for the Oxycodone HCL assay specification. The shelf life of mean dissolution at 4-hour using the original specification is longer than that using the revised specification.

Figure 1 Shelf life estimation of mean dissolution at 1 hour for 30 mg TR tablets in (b) (4) count bottles using the revised specification

Figure 2 Shelf life estimation of mean dissolution at 1 hour for 30 mg TR tablets in (b) (4) count bottles using the revised specification

Figure 3 Shelf life estimation of mean dissolution at 4 hour for 40 mg TR tablets using the revised specification

Table 4: Analysis of Oxycodone HCL assay and its dissolution based on up to 12 month stability data for 10, 15, 20, 30, 40 mg TR tablets using the revised specification

Strength	Parameter	Final model	Estimated shelf life, month	Estimated shelf life, month
10 mg	Dissolution at 1 hr	(b) (4)		
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
15 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
20 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
30 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			
40 mg	Dissolution at 1 hr			
	Dissolution at 4 hr			
	Dissolution at 12 hr			
	Oxycodone HCL Assay			

2.5 Statistical and Technical Issues

1). The sponsor's approach for poolability test for package slope was not acceptable.

2). The fact that the sponsor used the release observations as 0 package type is not acceptable. In the pooling test for slopes, there is only one observation for 0 package type and no release data used for (b) (4) 100, (b) (4) counts per package. If the slopes can be pooled, the release data is used in the regression line. If the slopes cannot be pooled, the release data is ignored in estimation of shelf-life.

3). The shortest estimated shelf from (b) (4), listed in Table 2, is (b) (4), not 24 months. Hence the 24-month shelf life was not established by the sponsor.

4). The sponsor provided 12-month stability update for the 100 count bottles only. The other (b) (4) packages have 9 month data. Based on the ICH Q1E, the shelf-life is up to 2* X (length of month available data), but not exceeding X+ 12 months, or if refrigerated up to 2*X, but not exceeding X+6, if long-term data, if amendable to statistical analysis and statistical analysis is performed,
a) For 100 counts per package, the shelf-life is (b) (4) months;
b) (b) (4)
c) If the product needs to be refrigerated (I could not confirm this), the shelf life is (b) (4) for the 100 count package (b) (4)

2.6 Statistical Evaluation of Collective Evidence

The reviewer performed independent stability analyses for the assay data and the dissolution data at 1 hour, 4 hours, and 12 hours of Oxycodone. Based on these analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through (b) (4) months when the revised specification is used and the product is stored at 25^0C/60% RH.

2.7 Conclusions and Recommendation

Based on this reviewer's analyses and evaluations of Oxycodone data, the product is expected to remain within specifications through (b) (4) months when the revised specification is used and the product is stored at 25^0C/60% RH.

The sponsor provided a 12-month stability update only for the 100 count bottles. The other (b) (4) packages have data for only 9 month. Based on the ICH Q1E, the shelf-life is up to 2* X (length of month available data), but not exceeding X+ 12 months, or if refrigerated up to 2*X, but not exceeding X+6, if long-term data if amendable to statistical analysis and statistical analysis is performed,
1) For 100 counts per package, the shelf-life is (b) (4) months;
2) (b) (4);
3) If the product needs to be refrigerated (I could not confirm this), the shelf life is (b) (4) for the 100 count package (b) (4)

The sponsor's request for 24 month shelf life is not established.

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