CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-588

Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION
STABILITY REVIEW

Medical Division: Oncologic Drug Products (HFD-150)
Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER:	21588
SERIAL No:	Original NDA
DATE RECEIVED BY CENTER:	December 16, 2002
DRUG NAME:	Gleevec
PACKAGING:	90cc HDPE bottle (100 count for 100mg tablets and 30 count for 400 mg tablets)
STORAGE CONDITIONS:	Primarily 25° C with 60% RH
INDICATION:	CML
SPONSOR:	Novartis Pharmaceutical Corporation
DOCUMENTS REVIEWED:	Vol. 4 (abridged pages 270-320)
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Table of Contents

STATISTICAL REVIEW AND EVALUATION
STABILITY REVIEW

1. EXECUTIVE SUMMARY

1.1 CONCLUSION AND RECOMMENDATION

Measurements were taken at 0, 3, 6, 9 and possibly 12 months. All assay measurements were within specifications. The data for the 100 mg tablets support a shelf life of [ ] The data for the 400 mg tablets support a shelf life of [ ]

For the 100 mg tablets stored at 25° C with 60% RH, there was a statistically significant difference at the 0.25 significance level (p-value = 0.173) for testing for different batch slopes of the least squares lines for assay of active ingredient (%) by HPLC (based on the assumption of unequal intercepts). The fitted model involves three separate lines with a common residual variance. Because some batches, in fact most batches, have positive slopes for their assay least squares regression line, shelf-life calculations were based on two-sided 95% confidence bands for the regression lines. For batch X338 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X339 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X039 0202, the upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X039 0202, the initial assay of active ingredient was [ ] which was the lowest observed assay of active ingredient among all such measurements.

For the 400 mg tablets stored at 25° C with 60% RH, there was a statistically significant difference at the 0.25 significance level (p-value = 0.130) for testing for different batch slopes of the least squares lines for assay of active ingredient (%) by HPLC (based on the assumption of unequal intercepts). The fitted model involves three separate lines with a common residual variance. Because some batches, in fact most batches, have positive slopes for their assay least squares regression line, shelf-life calculations were based on two-sided 95% confidence bands for the regression lines. For batch X340 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X341 1101, the upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X040 0202, the upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. The lowest observed assay of active ingredient was [ ] observed for the 12-month value for batch X340 1101.

In summary, the maximum shelf life for the 100mg tablets is currently [ ] as estimated by batch X039 0202 and for the 400mg tablets is currently [ ] as estimated by batch X340 1101.

1.2 OVERVIEW OF STABILITY STUDIES

The stability data submitted for Gleevec 100 mg and 400 mg film coated tablets include measurements for up to nine months for full scale batches and twelve months for pilot batches at 25° C with 60% relative humidity (RH), for six months under accelerated conditions at 40° C with 75% RH, for six months at -20° C and 5° C and for one month at 50° C.

The sponsor concludes that there were no significant changes observed for the samples stored at these conditions and data were within specifications. The sponsor only provided a summary of the data; they did not perform any statistical analysis (model fitting, confidence intervals, or hypotheses testing).

This review will concentrate on the stability data under the conditions of 25° C and 60% RH. Three batches of Gleevec 100 mg (400 mg) tablets were studied. Measurements for all three batches per strength were taken at day 0, 3 months, 6months and 9 months, and measurements for two batches were taken at 12 months. These measurements fall short of the required 12 months data for at least three batches.

The 100 mg (400 mg) tablets were packed as 100 (30) tablets in 90cc HDPE bottles.

Table 1.2.1 gives a summary of some basic information about the batches studied.

Table 1.2.1 Batch summary

Batch Strength	Date of Manufacture (month year)	Batch type	Site of manufacture	Batch size [units]	Drug substance batch
X338 1101 100 mg	Nov 01	Pilot scale	Basel / CH	[redacted]	[redacted]
X339 1101 100 mg	Nov 01	Pilot scale	Basel / CH	[redacted]	[redacted]
X039 0202 100mg	Feb 02	Production scale	Basel / CH	[redacted]	[redacted]
X340 1101 400 mg	Nov 01	Pilot scale	Basel / CH	[redacted]	[redacted]
X341 1101 400 mg	Nov 01	Pilot scale	Basel / CH	[redacted]	[redacted]
X040 0202 400mg	Feb 02	Production scale	Basel / CH	[redacted]	[redacted]

All packaging used HPDE bottles. These bottles were white, square, high density polyethylene bottles (90 ml) with aluminum induction seal and child resistant polypropylene screw cap closure.

2. *DETAILED STABILITY REVIEW*

2.1 STABILITY STUDIES PROGRAM

The sponsor reported that no deviations from the protocol occurred.

The long term testing program had conditions of a temperature of 25° C with 60% RH for a planned study duration of [ ] with optional testing for [ ] months. The accelerated testing program had conditions of a temperature of 40° C with 75% RH for a planned study duration of 6 months. Testing was done under additional conditions with ambient RH having temperatures -20° C, 5° C and 50° C for respective study durations of 6 months, 6 months and one month.

Photostability testing used [ ] Parallel samples were stored under normal conditions (25° C). One batch per dosage strength was tested using : [ ]

A microbial limit test was performed with one batch per dosage strength and packaging at the initial time point and after six months storage. This test was planned to be performed at the end of the anticipated shelf life at 25° C with 60% RH.

2.2 REVIEW OF ASSAY DATA

2.2.1 Sponsor's Results

The sponsor concludes that there were no significant changes observed for the samples stored at these conditions and data were within specifications. The sponsor concludes that both drug product strengths are chemically and physically stable in the tested packaging type, that there was no observed change in photostability between exposed and unexposed samples and that there was no observed microbiological change (all batches complied with the requirements at the initial time point and after six months storage at 25° C with 60% RH).

The sponsor concludes that there was no significant increase of degradation product and no significant assay decrease. Additionally, the sponsor concludes that were no significant observed dissolution rate changes for stability testing under stress for both accelerated and long-term storage conditions. The sponsor also concludes that based on these stability results, "*the demonstrated stability of film-coated tablets is similar to capsules.*"

The sponsor states the following (vol. 4 page 281): *"All results in this registration stability report are within the specification and have shown very little variability. Compared to the initial values there is no significant change and no indication for any degradation. Therefore and also in accordance with the ICH guideline Q1AR a statistical analysis of the data was considered not necessary."*

The sponsor proposes an initial [ ] expiration date for Gleevec 100mg and 400mg tablets packaged in the intended commercial package, 90 cc HPDE bottles for trade (100mg tablets: 100 count; 400 mg tablets: 30 count). The bottles have a child resistant plastic cap closure with an induction seal. The storage requirements are: Do not store above 30° C and Protect from moisture. Store at 25° C allowing for excursions to 15° C - 30° C.

Reviewer's Comments:

1. Similarity or "equivalence" in the stability of the film-coated tablets and the stability of the capsules has not been tested. Therefore, it has not been demonstrated that the stability of the film-coated tablets and the stability of the capsules are similar or "equivalent."

2. The sponsor only provided a summary of the data; they did not perform any statistical analysis (model fitting, confidence intervals, or hypotheses testing).

Table 2.2.1.1 below gives the sponsor's summary of the chemical data for batches of 100mg tablets stored at 25° C with 60% RH.

Table 2.2.1.1 Sponsor's Summary of Chemical Data for batches of 100 mg tablets stored at 25° C with 60% RH

Strength Batch Packaging	Storage Conditions	Assay of active Ingredient (%) by HPLC	Degradation products	
			Each Individual (%)	Sum (%)
100 mg X338 1101 HDPE 90/100	Initial analysis	[		
	3 months			
	6 months			
	9 months			
	12 months			
100 mg X339 1101 HDPE 90/100	Initial analysis			
	3 months			
	6 months			
	9 months			
	12 months			
100 mg X039 0202 HDPE 90/100	Initial analysis			
	3 months			
	6 months			
	9 months			

Table 2.2.1.2 below gives the sponsor's summary of the chemical data for batches of 400mg tablets stored at 25° C with 60% RH.

Table 2.2.1.2 Sponsor's Summary of Chemical Data for batches of 400 mg tablets stored at 25° C with 60% RH

Strength Batch Packaging	Storage Conditions	Assay of active Ingredient (%) by HPLC	Degradation products	
			Each Individual (%)	Sum (%)
400 mg X340 1101 HDPE 90/30	Initial analysis	[		
	3 months			
	6 months			
	9 months			
	12 months			
400 mg X341 1101 HDPE 90/30	Initial analysis			
	3 months			
	6 months			
	9 months			
	12 months			
400 mg X040 0202 HDPE 90/30	Initial analysis			
	3 months			
	6 months			
	9 months			]

For both 100 mg and 400 mg tablets, all assay of active ingredient were between [ ] and [ ] and all degradations were within specifications.

Tables 2.2.1.3 and 2.2.1.4 below give a sponsor's summary of the physical data for batches of 100mg tablets stored at 25° C with 60% RH.

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Table 2.2.1.3 Sponsor's Summary of Physical Data for batches of 100 mg tablets stored at 25° C with 60% RH

Strength Batch Packaging	Storage Conditions	Appearance	Disintegration time (%) Average (n) [min, max]	% Loss on Drying
100 mg X338 1101 HDPE 90/100	Initial analysis	Complies *		-
	3 months	No change		
	6 months	No change		
	9 months	No change		
	12 months	No change		
100 mg X339 1101 HDPE 90/100	Initial analysis	Complies *		
	3 months	No change		
	6 months	No change		
	9 months	No change		
	12 months	No change		
100 mg X039 0202 HDPE 90/100	Initial analysis	Complies *		
	3 months	No change		
	6 months	No change		
	9 months	No change		

* Color: very dark yellow to brownish orange, Shape: round with score on one side, Imprint: NVR on the other side

Table 2.2.1.4 Sponsor's Summary of Physical Data for batches of 100 mg tablets stored at 25° C with 60% RH

Strength Batch Packaging	Storage Conditions	Dissolution after 15 min. (%) Average (n) [min, max]	Dissolution after 20 min. (%) Average (n) [min, max]
100 mg X338 1101 HDPE 90/100	Initial analysis		
	3 months		
	6 months		
	9 months		
	12 months		
100 mg X339 1101 HDPE 90/100	Initial analysis		
	3 months		
	6 months		
	9 months		
	12 months		
100 mg X039 0202 HDPE 90/100	Initial analysis		
	3 months		
	6 months		
	9 months		

Reviewer's Comment:

1. The information provided by the sponsor for the dissolution after 15 minutes at nine months for Batch X339 1101 is incorrect. An average [ ] can not be outside of the range ([ ]).

Tables 2.2.1.5 and 2.2.1.6 below give a sponsor's summary of the physical data for batches of 400mg tablets stored at 25° C with 60% RH.

Table 2.2.1.5 Sponsor's Summary of Physical Data for batches of 400 mg tablets stored at 25° C with 60% RH

Strength Batch Packaging	Storage Conditions	Appearance	Disintegration time (%) Average (n) [min, max]	% Loss on Drying
400 mg X340 1101 HDPE 90/30	Initial analysis	Complies *		-
	3 months	No change	[	
	6 months	No change		
	9 months	No change		
	12 months	No change		
400 mg X341 1101 HDPE 90/30	Initial analysis	Complies *		
	3 months	No change		
	6 months	No change		
	9 months	No change		
	12 months	No change		
400 mg X040 0202 HDPE 90/30	Initial analysis	Complies *		
	3 months	No change		
	6 months	No change		
	9 months	No change		]

* Color: very dark yellow to brownish orange, Shape: round with score on one side, Imprint: NVR on the other side

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Table 2.2.1.6 Sponsor's Summary of Physical Data for batches of 400 mg tablets stored at 25° C with 60% RH

Strength Batch Packaging	Storage Conditions	Dissolution after 15 min. (%) Average (n) [min, max]	Dissolution after 20 min. (%) Average (n) [min, max]
400 mg X340 1101 HDPE 90/30	Initial analysis	[redacted]	
	3 months		
	6 months		
	9 months		
	12 months		
400 mg X341 1101 HDPE 90/30	Initial analysis		
	3 months		
	6 months		
	9 months		
	12 months		
400 mg X040 0202 HDPE 90/30	Initial analysis		
	3 months		
	6 months		
	9 months		

All initial values for dissolution after 20 minutes were tested after 30 minutes and may give unduly high results. All disintegration times were shorter than 20 minutes, meeting the set requirement. All dissolution values were far greater than [ ] easily meeting this specification.

2.2.2 Reviewer's Results

For the 100 mg tablets stored at 25° C with 60% RH, there was a statistically significant difference at the 0.25 significance level (p-value = 0.173) for testing for different batch slopes of the least squares lines for assay of active ingredient (%) by HPLC (based on the assumption of unequal intercepts). The fitted model involves three separate lines with a common residual variance. Because some batches, in fact most batches, have positive slopes for their assay least squares regression line, shelf-life calculations were based on two-sided 95% confidence bands for the regression lines. For batch X338 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X339 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X039 0202, the upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X039 0202, the initial assay of active ingredient was [ ] which was the lowest observed assay of active ingredient among all such measurements.

For the 400 mg tablets stored at 25° C with 60% RH, there was a statistically significant difference at the 0.25 significance level (p-value = 0.130) for testing for different batch

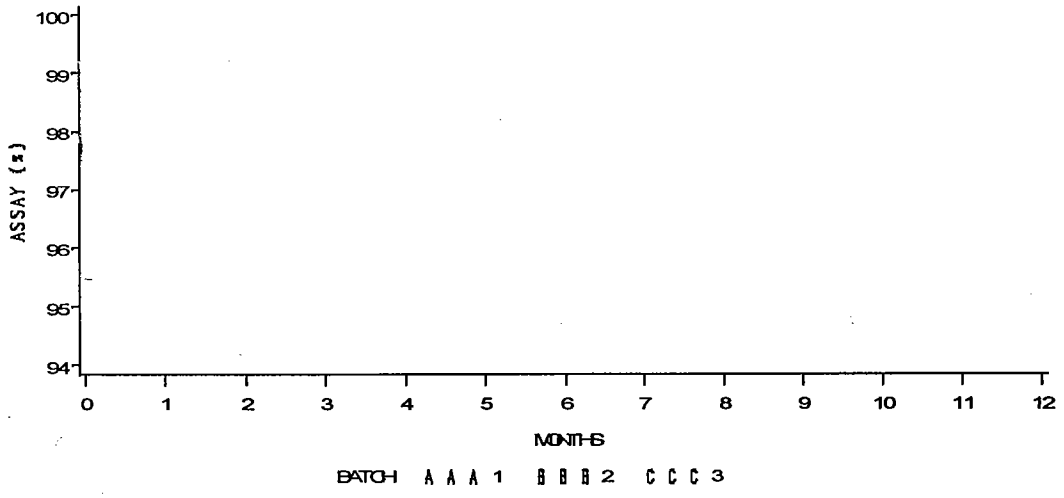
slopes of the least squares lines for assay of active ingredient (%) by HPLC (based on the assumption of unequal intercepts). The fitted model involves three separate lines with a common residual variance. Because some batches, in fact most batches, have positive slopes for their assay least squares regression line, shelf-life calculations were based on two-sided 95% confidence bands for the regression lines. For batch X340 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold [ ] months. For batch X341 1101, the upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X040 0202, upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. The lowest observed assay of active ingredient was [ ] observed for the 12-month value for batch X340 1101.

3. *APPENDIX 1: GRAPHS OF EXPIRY DATE ESTIMATION*

3.1 FIGURE FOR 100 MG UNDER STORAGE CONDITIONS OF 25° C WITH 60% RH

Figure 1 below gives the scatterplot of the percent assay versus months for three batches exposed to 25° C with 60% RH. Characters 'A', 'B' and 'C' respectively represent the points for batches X338 1101, X339 1101, and X039 0202. The lowest observed assay of active ingredient was the initial value of [ ] for batch X039 0202 HDPE 90/100.

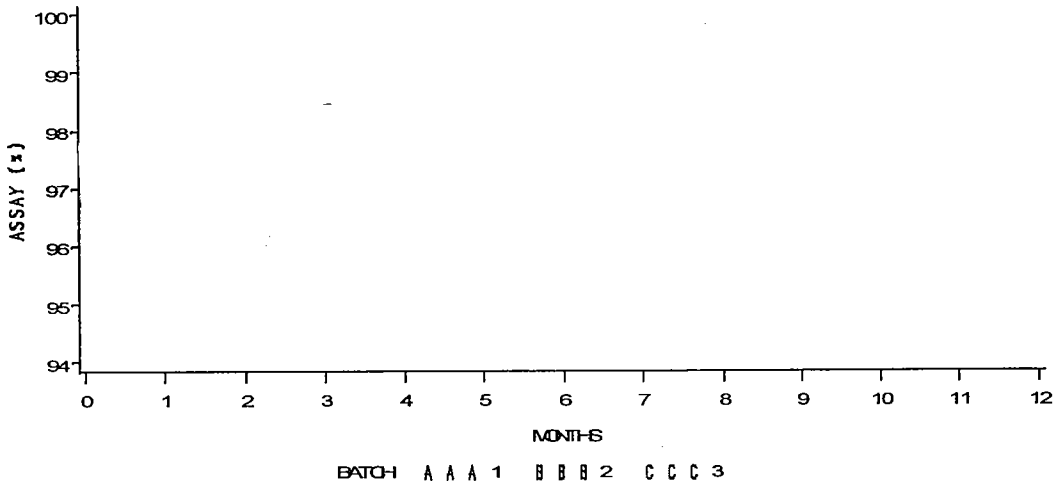
Figure 1. Scatterplot of the percent assay versus months for three batches exposed to 25° C with 60% RH.



3.2 FIGURE FOR 400 MG UNDER STORAGE CONDITIONS OF 25° C WITH 60% RH

Figure 2 below gives the scatterplot of the percent assay versus months for three batches exposed to 25° C with 60% RH. Characters 'A', 'B' and 'C' respectively represent the points for batches X340 1101, X341 1101, and X040 0202. The lowest observed assay of active ingredient was [ ] observed for the 12-month value for batch X340 1101 HDPE 90/30.

Figure 2. Scatterplot with regression line of percent assay versus months for three batches exposed to 25° C with 60% RH.



4. *APPENDIX 2: STATISTICAL METHODS FOR EXPIRATION DATE ESTIMATION*

4.1 GENERAL CONCEPT AND STABILITY STRUCTURE

The sponsor gives the requirements for the determination of degradation products as [ ] for each individual and [ ] altogether, and the requirements for the assay of active ingredient Gleevec by HPLC of not less than [ ], and not more than [ ]. The requirement for disintegration time is "not longer than 20 minutes." The acceptance plan USP for dissolution by UV is "Q = [ ] in 15 minutes (stage 1 and 2 only)."

4.2 STATISTICAL PROCEDURE

4.2.1 Step 1: "Poolability" of the Batches

For the 100 mg tablets stored at 25° C with 60% RH, there was a statistically significant difference at the 0.25 significance level (p-value = 0.173) for testing for different batch slopes of the least squares lines for assay of active ingredient (%) by HPLC (based on the assumption of unequal intercepts). The fitted model involves three separate lines with a common residual variance.

For the 400 mg tablets stored at 25° C with 60% RH, there was a statistically significant difference at the 0.25 significance level (p-value = 0.130) for testing for different batch slopes of the least squares lines for assay of active ingredient (%) by HPLC (based on the assumption of unequal intercepts). The fitted model involves three separate lines with a common residual variance.

4.2.2 Step 2: Regression Analysis for Expiry Estimation

Because some batches, in fact most batches, have positive slopes for their assay least squares regression line, shelf-life calculations were based on two-sided 95% confidence bands for the regression lines. For batch X338 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X339 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X039 0202, the upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X039 0202, the initial assay of active ingredient was [ ] which was the lowest observed assay of active ingredient among all such measurements.

Because some batches, in fact most batches, have positive slopes for their assay least squares regression line, shelf-life calculations were based on two-sided 95% confidence bands for the regression lines. For batch X340 1101, the lower band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X341 1101, the upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. For batch X040 0202, upper band of the two-sided 95% confidence bands intersected an assay of active ingredient threshold of [ ] months. The lowest observed assay of active ingredient was [ ] observed for the 12-month value for batch X340 1101.

This review consists of 13 pages. 3/21/03.

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/s/

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