

# Approval Memo - RECOTHROM

## MEMORANDUM

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Biologics Evaluation and Research

**Date:** December 21, 2007

**To:** Mark Shields, HFM 380 and File STN 125248

**From:** Roman Drews, HFM-392

Review Committee Chair

**Through:** Timothy Lee, HFM-392

Acting Chief, Laboratory of Hemostasis, DH, OBRR

**Subject:** Approval of Biological License Application from ZymoGenetics, Inc. for Thrombin, topical (Recombinant), (rThrombin), [RECOTHROM®];

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This biologics license application was reviewed by a committee that included the following CBER reviewers: Dr. Paul Aebersold (Clinical), Dr. Paul Buehler (Pharmacology/Toxicology), Mr. Sean Byrd (Facility inspector), Dr. Roman Drews (CMC/Chairperson), Ms. Maryann Gallagher (Advertising and Labeling), Mr. Myke Hall (Electronic integrity), Dr. Paul Hsieh (Biostatistics), Dr. Nisha Jain (Clinical), Dr. Nancy Kirschbaum (CMC), Ms. Eleanor Koo (CMC), Dr. Timothy Lee (CMC consult), Dr. Kimberly Lindsey (Clinical), Ms. Carolyn Renshaw (Facility consult), Mr. Mark Shields (Administrative/Regulatory), Ms. Nancy Waites (CMC/Facility), and Ms. Janet White (Bioresearch monitoring). Based on the data submitted by ZymoGenetics, the review committee found the safety, potency, and efficacy of RECOTHROM to be acceptable and recommends approval of the BLA STN 125248.

### **Final Review for Chemistry, Manufacturing, Controls (CMC)**

#### **Background**

This memorandum summarizes the reviews of ZymoGenetics' (Zymo) responses to CMC information requests (IR) that were communicated to the firm during the review. The IR included issues raised by Dr. Nancy Kirschbaum and this reviewer. I found Zymo's response adequate. The stability data submitted by the firm support storage of final drug product up to 24 month at 2°C to 25°C and ----- (the supportive information is available in the review memorandum provided by Mrs. Eleanor Koo and the stability data update submitted to the FDA on December 21, 2007). Although RECOTHROM is a well characterized, recombinant DNA-derived product, it is the first recombinant product in the market. Therefore, RECOTHROM is put under a CBER surveillance program, which will be revised when more manufacturing experience will be acquired. Finally, Zymo committed to address all post-marketing commitments (PMC) that have been discussed between the firm and CMC reviewers. Thus, there are no outstanding CMC issues that are preventing approval of STN 125248.

**Regarding the post-production cell ----, please provide:**

- Regarding the production bioreactor:**

- [illegible]



process control testing for the manufacturing process. The necessity of these tests can be evaluated periodically when more data are available.

Tests assessing -----

--- will be included as in-process controls for commercial manufacture of -----.

These additional tests are considered as non-critical in process controls, and have associated action limits resulting in an investigation if the action limits is exceeded. As requested by CBER, the analytical paradigm provides assessment of the -----

-----

----- standard material, will be performed by Zymo. The action limits were established based on the manufacturing experience with conformance lots and additional validation studies. The provided response is acceptable.

2. *In addition, please provide the current standard operating procedures for the investigation of deviations in action limits.*

The information provided by Zymo is acceptable.

**Regarding the ----- columns:**

1. *The validation runs performed at commercial and small scale demonstrate that the -----*

-----.

----- However, the proposed action limit for the -----

----- Please describe how you derived the proposed action limit.

Zymo stated that the ----- action limit was determined with data from small-scale and scale up studies, and ----- commercial process runs. The analysis of eight samples resulted in -----

. ----- However, as

indicated in the provided Table 1, the yield values determined at small-scale -----

----- when compared to the values obtained at scale-up and production runs -----

artificially ----- the proposed limit. Considering that by now more lots of rThrombin were manufactured at the commercial scale, Zymo should proposed a new limit that truly reflects the production values. -----

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----- Thus, it is important that the limit for -----

-- operation is compatible with capacity of the manufacturing process performed at commercial scale.

Zymo submitted satisfactory response. Based on the commercial scale manufacturing data (including process variability), the firm proposed alert limit of ----- for yield of . -----

2. *The Acceptable Operating Range for the combined ----- chromatography load has been proposed as ----- However, the critical parameters studies, based on validation runs, estimated the Acceptable Operating Range as ----- Please describe how you derived the proposed load limit of -----.*

Zymo explain that proposed load limit of ----- has been established based on the capacity of the -----, confirmed at small-scale studies, and size of the ----- chromatography column, ----- . The Acceptable Operating Range of ----- has been established based on ----- and the validation studies, i.e. operational capacity of the ----- chromatography column, ----- . The response provided by Zymo is acceptable.

3. *Please establish an in-process control parameter for ----- yield expressed in -----.*

Zymo pointed out that the current rThrombin manufacturing process has acceptance limits for the operation of ----- columns based on -----, where the amount of ----- . The minimum acceptable amount of ----- . The firm committed to introduce in-process control parameter that will be used to measure ----- . A calculation to express ----- will be added to the batch record. It will be quantitated using ----- . An in-process control associated with this calculation will define an action limit that the ----- must meet ----- . Therefore, the action limit will be calculated from the ----- , ----- . The proposed change is acceptable. ----- .

**Regarding process operational parameters:**

1. *Please explain the difference between the following terms: Acceptable Operating Range, Acceptance Criteria, and Action Limit in relation to the control of operation unit performance. Please describe also the difference in investigational procedures and resultant actions when the limits defined by these terms are breached.*

The response provided by the firm is acceptable. The Acceptable Operating Range (AOR) has been established ----- . AOR are usually ----- . Acceptance criteria are ----- . Action Limits define ----- .

**Regarding Methods Validation:**

1. *Regarding validation of your ----- Activity assay:*  
a. *For accuracy experiments:*

- i. *You stated that assays 1-2 were performed from one set of preparations on day 1 and assays 3-6 were performed from a second set of preparations on day 2; yet, you chose to perform analyses on pooled values from assays 1-3 separately from assays 4-6. Please comment.*

Zymo explained that per validation protocol three sets of samples with three concentrations were to be run in 6 analyses over 2 days. But due to the technical problem the laboratory could not perform all planned assays on the first day. The protocol mentioned performing the accuracy experiment over 2 days in different then originally scheduled sequence. The results were pooled due to statistical plan that require an average of three reportable results. I agree with the firm's opinion that this deviation from validation report did not affect final results of the accuracy parameter.

- ii. *You claimed that----- experiments were performed; however, you ----- rather than supplementing another--- preparation that had a pre-determined concentration. Please comment.*

Zymo stated that used -----in the ----- studies. The ---- samples were used because ----- . The assay procedure requires ----- to reach the assay's range. The study evaluated the effect of having ----- present in thrombin in the final ----- test sample. The recovery was ----- with relative standard deviation of ----- that met validation acceptance criteria. The provided response is adequate.

b. *or repeatability experiments:*

- i. *Please clarify the origin of the ----- values used for each concentration level.*

The ----- assay was developed to test samples in the ----- . Samples are tested in ----- at ----- in -- separate and independent analyses. Potency is an ----- of the -- values generated in each analysis. The proposed approach is adequate.

- ii. *Please clarify the relationship of Table 2 values to Table 4 values.*

The firm explained that Table 2 consists of ----- results from the first -- analysis runs (-----) that are average of the results of the ----- in analysis. Table 4 was presented to demonstrate repeatability between tested samples and include raw data from ----- only. Runs ---- were performed in a similar manner but results were not use to support repeatability experiment. The provided explanation is adequate.

c. *For intermediate precision experiments:*

- i. *Please clarify the relationship between Table 2/3 values and Table 5 values.*

Zymo satisfactory explained the observed discrepancy. Values presented in Table 2/3 are average values of all 7 analyses. Table 5 presented all reportable results for each preparation. In its response, Zymo submitted additional table demonstrating the reportable results, i.e. data from 3 runs for each of the 3 concentrations tested for the intermediate precision.

d. *For non-product specificity experiments:*

i. *Please provide a summary of studies that supported the -----*  
-----.

Zymo explained that ----- was not used. Zymo calculated -----

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----- The submitted response is acceptable.

e. *For lower limit of detection and linearity/range experiments:*

i. *Please identify the reference standard used to generate standard curves.*

Zymo confirmed that the standard curves were generated with the -----  
standard material, -----, which was described in the original BLA  
(Section 3.2.S.5) and found to be acceptable.

f. *Please submit the study report from validation of your assay with reference to the --*  
*----- concentrates ----- . Please submit*  
*the study report from calibration of your -----*  
*----- with reference to the ----- concentrates.*

The requested report was submitted by Zymo. Report RES-10810 describes the results of conversion from the US (NIH) units that were initially used by ZGI to assess potency of rThrombin by the ----- Activity Assay to the International Standard Units (IU). ZGI used the current International Reference Standard (-----  
----- obtained from National Institute for Biological Standards and Control) to calibrate their ----- standard material ----- The executed testing plan included --- independent assays. ----- different preparations of human fibrinogen and ----- samples (in -----) of ----- of ----- reference material were used in the assays. The studies were performed for ----- days by --  
----- analysts. The statistical analyses included ANOVA test, and mean (IU/mL), standard deviation (SD), and percent of relative standard deviation (%RSD) were established. The study resulted in calibration of the ----- reference material. The assigned potency is -----, overall Specific Activity -----, overall %RSD ----- The theoretical specific activity (based on NIH U/mg) equals -  
--- The ----- The performed studies are acceptable.

g. *Please validate your assay to demonstrate parallelism between reference curve and sample ----- series.*

Please see response to Question "1 i".

h. *Please describe control charting procedures you have implemented for monitoring routine performance of the ----- Activity assay using a routine assay control preparation (different from reference standard, -----).*

Zymo submitted control charting procedure. It indicates that control samples were -  
----- from the reference material ----- . Zymo committed to -----  
-----

- i. *Please validate your assay for determination of thrombin potency for release of final drug product (i.e. please test final container product in validation experiments).* The submitted report QCTM -038 covers validation study for rThrombin final drug product (FDP) and includes requested parallelism experiment between reference curve and sample ----- series. The provided results are acceptable. The study encompasses 5000 IU ----- of the final product. The 5000 IU product presentation was reconstituted according to instructions provided in Full Prescribing Information in label, i.e. 0.9% Sodium Chloride Injection USP and using provided kit. As demonstrated in the table below, the tested parameters of the validation studies were fulfilled and results are acceptable. Lots of rThrombin at different stages of stability were tested in the referenced studies. Following the Pre-Approval Inspection recommendations, linearity parameter of standard curve has been determined (R-squared of -----.



[illegible]

The parallelism conformation studies were performed between reference material, released and ----- sample of rThrombin. ---- runs with ---- curves were performed. The slope of each standard curve was compared to standard material as a ratio. The evaluation of ----- sample, which have ----- by ----- relative to standard curve was performed to observed non-parallelism. The results show that acceptable parallelism was observed for all tested samples, included ---- -- samples. Zymo stated that results of the study indicate that parallelism is not affected by the ----- . The example of parallelism run is enclosed below.

In addition, the content uniformity has been assessed using the newly validated potency assay. Ten vials of rThrombin FDP reconstituted with 0.9 % NaCl were analyzed (-----) by the ----- by --- analysts. The results demonstrated that no individual vial was outside of the ----- (---- IU/vial) to ----- (- --- IU/vial) acceptance criteria (with target limit of content ----- IU/vial) and all relative SD values stayed within acceptance criteria of -----.





[illegible]

The concentration of Histidine in rThrombin FDP is measured by -----  
-----  
-----, The details of validation study are enclosed below.

[illegible]



DETERMINED

TO BE

NOT RELEASABLE

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**Regarding the Proposed Specification for Bulk Drug Substance (BDS):**

1. Please establish acceptance ranges for -----.

Zymo's strategy to control -----

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----- Therefore, I agree with the ZGI opinion that it is more appropriate to control the -----.

Proposed 5000-IU lyophilized ----- drug product specifications are shown below. The proposed specification limits were established based on analytical results from --- lots, i.e. qualification, Phase-3 clinical lots and additional lots manufactured at commercial scale applying + SD statistical model.

**----- Acceptance Criteria**

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The proposed specification limits are acceptable.

2. Please establish an acceptance limit for -----.

Zymo presented additional data demonstrating that -----

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----- I agree with Zymo assessment that results of testing for ----- obviate the need for the acceptance limit.

3. *Please establish an acceptance range for ----- since it is a critical process parameter that guides further manufacture.*

The response provided by the firm is acceptable. Based on the manufacturing experience and current acceptance limit for the -----, ZGI proposed the following limits for -----.

4. *Please retain your established acceptance limit for ----- since reporting the removal of this ----- is critical to assurance of product safety.*

In its response, Zymo proposed to not include acceptance limit for ----- justifying its decision by -----

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----- However, in the opinion of this reviewer the acceptance limit for the --

----- content should be maintained to assure consistency of the -----

process to ----- With more manufacturing experience gained in the

future, Zymo may request to terminate the -----, if

supported by the collected data. Zymo agreed with this recommendation and

specification is retained for product licensure.

***Revised Specifications for rThrombin BDS***

The revised specifications are acceptable. For details please see table below.

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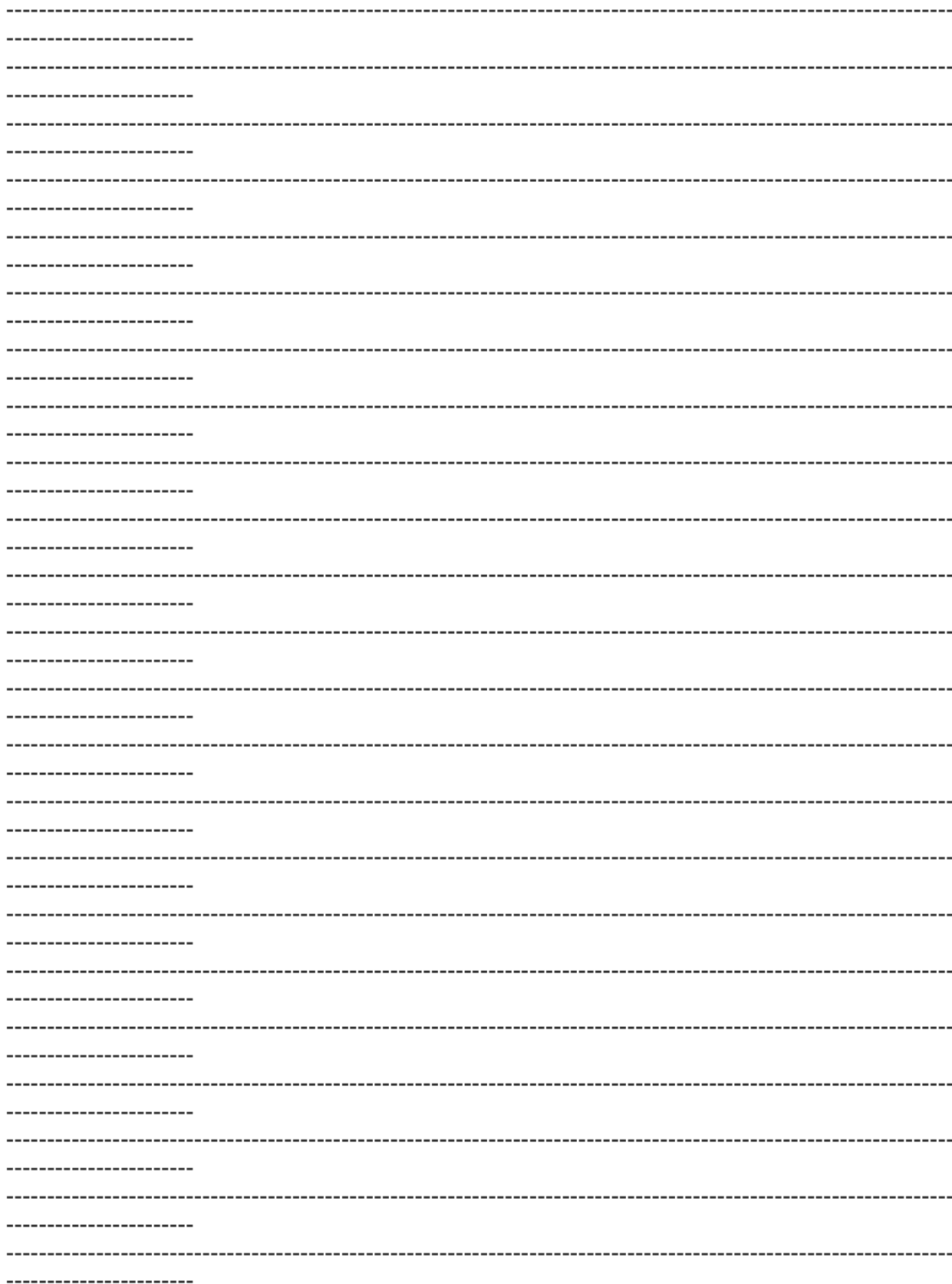


***Regarding the Proposed Release Specification for Final Drug Product (FDP):***

- The requested data has been provided in the validation report for the ----- assay (Report QCTM-038) i.e. the release specification reflects reconstitution in 5 mL of 0.9% NaCl. For details, please see response to the questions concerning method validation.

- Zymo pointed out that Guideline for the Determination of Residual Moisture in Dried Biological Products (1990), used by FDA to justify ----- limit, states that thrombin products should not exceed 3.0% residual moisture determined by the gravimetric or loss on drying test. The rThrombin residual moisture is determined by -----

[illegible]



The newly submitted data set demonstrates that rThrombin FDP manufactured at commercial scale should be stable at the proposed ----- residual moisture specification limit. -----

3. Please establish a release range for thrombin potency that defines an upper and lower limit. The lower limit should be established such that release at the lower limit will assure compliance with the end of shelf life requirement.

Lower potency limit = -----

Upper potency limit = -----

The lower potency limit is justified by -----

4. Please re-establish the content uniformity specification with respect to thrombin potency.

The requested data has been provided in the validation report for the ----- assay (Report QCTM-038). For details, please see response to questions concerning method validation.

5. Please establish a release range for specific activity relative to ----- rather than -----.

Zymo proposed a release range for specific activity relative to ----- for rThrombin FDP of ----- . The justification for the new limits is based on the data obtained from the manufacturing experience and ----- , and results of potency testing. The release specification is revised and implemented for the commercial lots.

6. Please establish a release range for the content of each excipient.

Please see Zymo response to the question concerning -----  
-----

7. Please provide further justification for the acceptance criterion, ----- stated as part of the Appearance specification. Please provide evidence that a reconstituted final product that is ----- does not contain denatured protein precipitate.

[illegible]

-. This is acceptable.

8. Please re-state the purity specification, ----- more accurately e.g. -----

Zymo revised the rThrombin FDP purity specification to state: -----  
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9. Please submit the release specification for the 0.9% NaCl diluent.

[illegible]

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The specifications are acceptable. For details please see table below.

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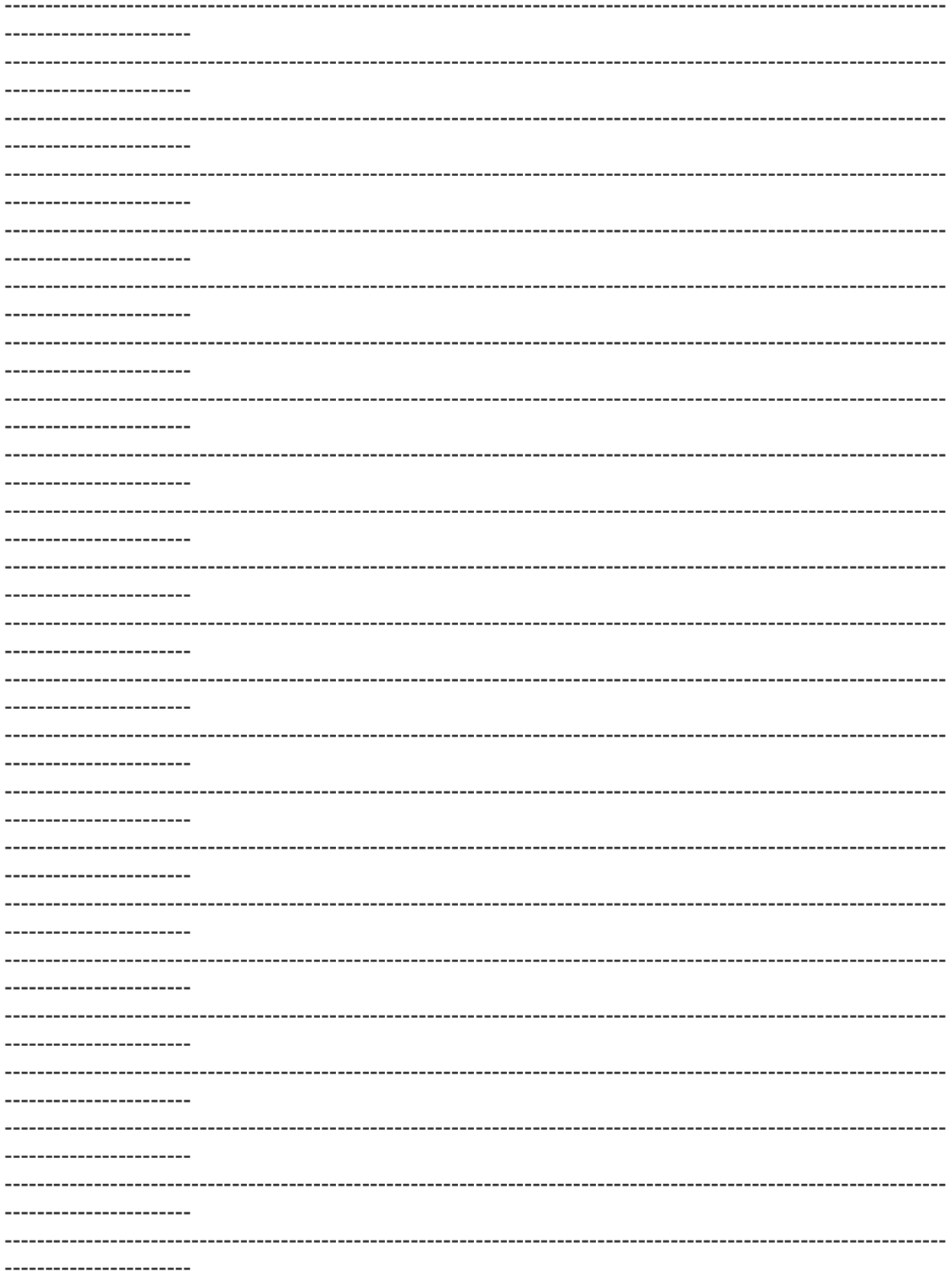
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**Recommendation**  
**Approval**