

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761083Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # **761083**
PMR/PMC Set (####) **3299**
Product Name: **Hemlibra (emicizumab-kxwh)**
Applicant Name: **Genentech**
ODE/Division: **OHOP/DHP**

SECTION B: PMR/PMC Information

1. PMC #1 Description

Conduct an assessment of binding anti-product antibody (APA) responses with a validated assay capable of sensitively detecting APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient’s test sample at each sampling point.

2. PMC Schedule Milestones^{2, 3}

Final Report Submission: 01/2019

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

3. PMC #2 Description

Conduct an assessment of neutralizing anti-product antibody (APA) responses with a validated assay capable of sensitively detecting neutralizing APA responses in the presence of emicizumab levels that are expected to be present in the serum at the time of patient sampling. The neutralizing APA response will be evaluated in at least 50 emicizumab-treated patients. The final report will include information on the level of emicizumab in each patient's test sample at each sampling point.

4. PMC Schedule Milestones^{4, 5}

Final Report Submission: 12/2019

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁶ or clinical trial⁷ in the text box below.

The development of anti-product antibodies appears to affect the pharmacokinetics, safety and activity of emicizumab.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit [[Skip to Q.5](#)]
- Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit [[Skip to Q.5](#)]
- PREA PMR: Meets PREA postmarketing pediatric study requirements [[Skip to Q.5](#)]
- FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial [[Go to Q.3](#)]
- PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. [[Go to Q.3](#)]

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: [[Select all that apply](#)]

- Longer-term data needed to further characterize the safety/efficacy of the drug

⁴ Final protocol, study/trial completion, and final report submissions are required milestones. Draft protocol submissions and interim milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

⁵ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

⁶ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁷ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

4. **For FDAAA PMRs only** *[for PMCs skip to Q.5]. Complete this entire section*

a. **The purpose of the study/clinical trial is to:** *[Select one, then go to Q.4.b]*

- Assess a known serious risk related to the use of the drug
- Assess a signal of serious risk related to the use of the drug
- Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. **FAERS⁸ and Sentinel's postmarket ARIA⁹ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:**

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁸ FDA Adverse Event Reporting System (FAERS)

⁹ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient? *[Select either “Yes” or “No” and provide the appropriate responses.]*

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f. Because a study is not sufficient, a clinical trial is required. *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY
<input type="checkbox"/> Drug interaction or bioavailability studies (nonclinical only)
<input type="checkbox"/> Epidemiologic (observational) study related to safe drug use
<input type="checkbox"/> Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
<input type="checkbox"/> Immunogenicity study (nonclinical)
<input type="checkbox"/> Meta-analysis or pooled analysis of previous observational studies
<input type="checkbox"/> Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
<input type="checkbox"/> Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
<input type="checkbox"/> Pharmacogenetic or pharmacogenomic study
<input type="checkbox"/> Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
<input type="checkbox"/> Quality CMC study (e.g., manufacturing, studies on impurities)
<input type="checkbox"/> Quality stability study
<input type="checkbox"/> Registry-based observational study
<input type="checkbox"/> Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e. with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. **This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).**

- Yes
- No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):**

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements¹⁰

1. The PMR/PMC is clear, feasible, and appropriate¹¹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.
- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Insert electronic signature (usually the Deputy Director for Safety)

¹⁰ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

¹¹ See POLICY section of CDER MAPP 6010.9.

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/s/

BARRY W MILLER
11/09/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: November 8, 2017

Requesting Office or Division: Division of Hematology Products (DHP)

Application Type and Number: BLA 761083

Product Name and Strength: Hemlibra (emicizumab-kxwh) Subcutaneous Injection
30 mg/mL, 105 mg/0.7 mL, 60 mg/0.4 mL, and 150 mg/mL

Applicant/Sponsor Name: Genentech, Inc.

Submission Date: October 20, 2017 and October 31, 2017

OSE RCM #: 2017-1071-1

DMEPA Safety Evaluator: Casmir Ogbonna, PharmD, MBA, BCPS, BCGP

DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Hemlibra (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a Of note, the Patient Information Sheet was changed to a Medication Guide thus the statement "Attention: Dispense the enclosed Medication Guide to each patient" was added to carton labeling.

2 CONCLUSION

The revised container labels and carton labeling for Hemlibra are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Ogbonna, C. Label and Labeling and Human Factors Study Results Review for Hemlibra BLA 761083. Silver Spring MD: FDA, CDER, OSE, DMEPA US; 2017 MON 12. RCM No.: 2017-1071, and 2017-1570.

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/s/

CASMIR I OGBONNA
11/08/2017

HINA S MEHTA
11/08/2017

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 24, 2017

To: Laura Wall, Regulatory Project Manager, Division of Hematology Products (DHP)
Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for Hemlibra (emicizumab-kxwh) injection, for subcutaneous use

BLA: 761083

In response to DHP's consult request dated June 28, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Hemlibra.

PI and PPI/Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft Medication Guide, and IFU received from DHP (Laura Wall) via electronic mail on October 6, 2017 and the draft PI received via a Sharepoint link sent by electronic mail on October 17, 2017. OPDP's comments for the draft PI are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide and IFU were sent under separate cover on October 23, 2017.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room and received via a Sharepoint link sent by electronic mail from DHP (Laura Wall) on October 17, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
10/24/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 23, 2017

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Ruth Lidoshore, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Robert Nguyen, PharmD, Rph
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): HEMLIBRA (emicizumab-kxwh)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761083

Applicant: Genentech, Inc.

1 INTRODUCTION

On June 23, 2017, Genentech, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761083 for HEMLIBRA (emicizumab-kxwh) injection. The proposed indication is for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on June 27, 2017, and June 28, 2017, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for HEMLIBRA (emicizumab-kxwh) injection.

2 MATERIAL REVIEWED

- Draft HEMLIBRA (emicizumab-kxwh) injection MG and IFU received on June 23, 2017, and received by DMPP and OPDP on October 6, 2017.
- Draft HEMLIBRA (emicizumab-kxwh) injection Prescribing Information (PI) received on June 23, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 6, 2017 and October 17, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
10/23/2017

ROBERT L NGUYEN
10/23/2017

BARBARA A FULLER
10/23/2017

LASHAWN M GRIFFITHS
10/23/2017

Memorandum of Review

STN:	BLA761083
Subject:	Immunogenicity Review
Submission Date:	June 23, 2017
Review/Revision Date:	October 16, 2017
Primary Reviewer:	Haoheng Yan, MD, PhD (Immunogenicity assays) Product Quality Reviewer, OPQ/OBP/DBRR IV
Secondary Reviewer:	Bazarragchaa Damdinsuren, MD, PhD Team Leader, OPQ/OBP/DBRR IV
Tertiary Reviewer:	Joel Welch, PhD Acting Review Chief, OPQ/OBP/DBRR IV
Applicant:	Genentech
Product:	Emicizumab
Indications:	Treatment of patients with hemophilia A (congenital Factor VIII deficiency) with factor VIII inhibitors
Action Due Date:	November 15, 2017

Summary

Emicizumab (ACE910) is a humanized anti-factor IXa/X bispecific antibody. To evaluate the immunogenicity of emicizumab, the sponsor developed three anti-drug antibody (ADA) binding assays and one neutralizing antibody (NAb) assay. The three ADA binding assays include an electrochemiluminescence (ECL) based bridging assay used in testing phase 1 and 2 samples, an enzyme-linked immunosorbent assay (ELISA) based bridging assay used as reference to test confirmed ADA positive samples from phase 1 and 2, and a different ELISA based bridging assay used in testing phase 3 samples. All three assays use bridging format with minor difference in reagents' labelling and concentration. None of these binding assays shows sufficient sensitivity in the presence of expected on board plasma emicizumab ((b) (4) (b) (4) note that the recommended doses are 3 mg/kg/week for the first 4 weeks, followed by 1.5 mg/kg/week). The neutralizing antibody (NAb) assay assesses the neutralizing activity by measuring the increase of activated partial thromboplastin time (aPTT) in response to emicizumab in factor VIII-deficient plasma. The neutralizing assay is also inadequate due to insufficient drug tolerance. Therefore, all of the immunogenicity assays (ADA and NAb assays) used in the application are inadequate and assay results may not reflect the true immunogenicity property of emicizumab. We recommend the sponsor re-develop ADA assay(s) (screening, confirmatory and titer assays) and NAb assay as PMCs to evaluate the effect of ADA on PK, safety and efficacy. (b) (4)

(b) (4)

After discussion with the review team, it was determined that the inadequate assays and consequently the potential under-reported ADA and NAb rates do not preclude the approval of the BLA as the overall treatment benefits outweigh the risk. In addition, the clinical team determined that even with the assay limitations, the clinical studies do not reveal a clinical signal with regards to safety issues (e.g., hypersensitivity) that could correlate with ADAs. Therefore, the review team agrees with the immunogenicity studies (including the assay re-development) as PMCs.

Post Marketing Commitments (draft wording)

1. Develop and validate a sensitive and precise assay for the detection of anti-emicizumab antibodies (ADA). The assay should be capable of sensitively detect ADA responses in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include screening, confirmation and titer assay validation reports and assay SOPs.
2. Develop and validate an assay to evaluate the neutralizing capacity of ADA detected in the patient samples. The assay should be capable of sensitively detect neutralizing ADA in the presence of emicizumab levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay SOP.

Review

- Unless otherwise noted, figures and tables in this review are copied directly from the submission.
- The review sequence of the individual aspect of the assay validation may not follow the exact sequence in the submission.
- The "guidance" cited in the review refers to the "FDA Draft Guidance to Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins, April 2016"
<http://www.fda.gov/downloads/Drugs/.../Guidances/UCM192750.pdf>

Testing Strategy

The sponsor uses a tiered approach to detect anti-drug antibody (ADA) in clinical samples. Samples are first tested in an ADA screening assay, samples that screened positive are tested in a confirmatory assay. Confirmed positive sample are tested for titer and neutralizing antibody (NAb).

Reviewer's Comment: The sponsor's approach to evaluate ADA is adequate (per the guidance).

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Overall, the NAb assay is inadequate due to low assay sensitivity in the presence of expected on board emicizumab. We recommend the sponsor re-develop a NAb assay with adequate sensitivity to evaluate emicizumab immunogenicity.

After discussion with the review team regarding the sensitivities of the ADA and NAb assays, it was determined that the inadequate assays and consequently the potential under-reported ADA and NAb rates do not preclude the approval of the BLA as the overall treatment benefits outweigh the risk. Therefore, the review team agrees with the immunogenicity studies (including the assay re-development) as PMCs. Note that the clinical team determined that even with the assay limitations, the clinical studies do not reveal a clinical signal with regards to safety issues (e.g., hypersensitivity) that could correlate with ADAs. Therefore, the review team agrees with the immunogenicity studies (including the assay re-development) as PMCs. The clinical pharmacology reviewers recommend a PMC for testing the clinical samples using the re-developed and validated ADA and NAb assays.



Haoheng
Yan

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Welch

Digitally signed by Joel Welch
Date: 10/16/2017 08:06:23PM
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LABEL AND LABELING AND HUMAN FACTORS STUDY RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 12, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761083
Product Type:	Single Ingredient Product
Drug Constituent Name and Strength	Hemlibra (Emicizumab) Subcutaneous Injection 30 mg/mL, 105 mg/0.7 mL, 60 mg/0.4 mL, and 150 mg/mL
Device Constituent:	Single-dose 3 mL glass Vials
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genentech, Inc.
Submission Date:	May 31, 2017, and June 23, 2017
OSE RCM #:	2017-1071, and 2017-1570
DMEPA Primary Reviewer:	Casmir Ogbonna, PharmD, MBA, BCPS, BCGP
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director (Acting):	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review is in response to a consult from the Division of Hematology Products (DHP) for DMEPA to review the human factors (HF) validation study results submitted on June 23, 2017, for the proposed Hemlibra. In addition, we provide a review of the Instructions for Use (IFU), carton labeling, container labels, and prescribing information (PI). Genentech, Inc. submitted BLA 761083 for Hemlibra (emicizumab) as a 351(a) application as a rolling submission with part 1 on May 31, 2017 and part 2 on June 23, 2017.

1.1 PRODUCT INFORMATION

Hemlibra (emicizumab) is a recombinant humanized monoclonal modified immunoglobulin G4 (IgG4) Biphasic antibody factor IXa and factor X, indicated for the treatment of Hemophilia A in adult and pediatric patients. It is administered as a subcutaneous injection in a physician's office, outpatient clinic, or home. The Applicant proposes 4 vial dosage strengths: 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, and 150 mg/mL. Emicizumab is initiated at a dose of 3 mg/kg weekly for 4 weeks, followed by 1.5 mg/kg weekly as a maintenance dose. The preparation and administration of Emicizumab will require a syringe, transfer needle, and injection needle which are 510(k) cleared and commercially available. In some instances, the patient's dose may require the users to combine the contents of more than one vial.

1.2 REGULATORY HISTORY

Genentech, Inc. submitted a Human Factors (HF) Validation Study Protocol for emicizumab on July 8, 2016, under IND 122954^a. DMEPA reviewed the HF validation study protocol^b and provided comments to Genentech.^c We confirmed that the comments included in the DMEPA review were implemented.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C

^a Genentech Inc. Protocol for (IND 122954).

^b Garrison, N. Human Factors Protocol Review for emicizumab injection (IND 122954). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 Sep 13. RCM No. 2016-1577.

^c Wall L. COR-INDAD-02 Advice/Information Request for emicizumab. Silver Spring (MD): FDA, CDER, OND, DHP (US); 2016 Sep 15. IND 122954.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the human factors validation study results. We also performed a risk assessment of the proposed labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement.

3.1 HUMAN FACTORS VALIDATION STUDY:

Methodology

We reviewed the methodology in our previous review of the protocol^d. The summative human factors study was performed with a sample of 15 Healthcare Professionals (HCPs) and 33 lay users (patients and caregivers). Study participants included both injection experienced and injection naïve, pediatric (7-11 years, 12-17 years) and adult (18+yrs) lay-users. To reflect the intended use, all patients and caregivers were trained prior to self-injection; HCPs were not provided with training since all HCPs were professionally certified to perform injections. All participants completed two different use scenarios (one with dose preparation from a single vial and one with dose preparation from combining multiple vials) and a knowledge-based assessment. In addition, HCPs completed a labeling differentiation scenario which included carton and container packaging. The strength differentiation was between Hemlibra vial labels and secondary packaging artworks.

^d Garrison, N. Human Factors Protocol Review for emicizumab IND 122954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 7. RCM No.: 2016-1577.

Results

We have provided a summary of the results in the following sections.

1. Differentiation (HCPs only):

All (15/15) HCPs were able to correctly identify the product strength in two differentiation tests of the container (vial) label and carton (secondary packaging artwork) when presented with a prescription.

2. Simulated Injection: Table 2 lists the critical tasks where failures occurred, the number of errors that occurred during the task categorized by user group, our analysis of the errors, and a summary of our recommendations for each error.

Table 2. List of tasks where failures occurred and the number of failures that occurred during the task

Task	# of Errors by User Group	Analysis of Error	Recommendations
Adjusting the plunger to the prescribed dose (+/- 20%)	4 failures (1 patient and 3 caregivers)	3 of the errors occurred in the single vial scenario. Two participants did not follow the IFU. One participant used the bottom of the plunger to set the dose. Genentech determined the maximum deviation from acceptable range was 21.8% and a one-time deviation outside the +/- 20% acceptable range does not require medical intervention. All participants were able to set the correct dose in the subsequent scenario without re-training.	The IFU contains instructions and images of how to position and adjust the plunger to the prescribed dose. We confirmed with the medical officer that a one-time deviation of +/-20% would not be clinically significant. We note that none of the participants made this error in subsequent scenarios. Therefore, we do not have any recommendations to mitigate the risk for these errors and we find the residual risk acceptable.
Fully depressing the plunger	1 failure (caregiver)	Participant pulled the needle out of injection pad early then realized it was a mistake and re-inserted the needle for remainder of dose. A small drop was on the injection pad. Genentech determined that no harm would occur to patient as a small/negligible amount was not	The IFU clearly states that the plunger should be pushed all the way down. Additionally, the participant realized their error and attempted to self-correct. Therefore, we do not have any recommendations to

		delivered and residual risk was within acceptable limits.	mitigate the risk for these errors and we find the residual risk acceptable.
Activate needle safety shield	2 failures (1 patient and 1 HCP)	Both participants did not activate needle safety shield but safely disposed of the syringe and needle directly into the sharps container. Genentech determined it was a study artifact as participants stated they would do it correctly in real life. Genentech modified the IFU to bold the instruction to engage safety shield in the IFU.	We agree with the Sponsor that this use error was a study artifact and therefore, we do not have any recommendations to mitigate the risk for these errors and we find the residual risk acceptable. The IFU prominently communicates the instruction to engage safety shield.
Dispose of used syringe with attached needle and vials safely	17 failures	8 of the failures were the participants disposing the vials in the general trash instead of sharps. 9 of the participants removed the needle from the syringe before disposing them in the sharps, due to not reading the IFU. Of note, there were no needle sticks. Genentech modified the IFU to highlight the instruction to dispose of vials in sharps container in the IFU. In addition, an instruction not to detach the injection needle prior to disposal has been added.	The Applicant has modified the IFU to address the use errors observed with this task in the study. We agree with the modifications and do not have any further recommendations to mitigate the risk for these errors. We find the residual risk acceptable.
Remove transfer needle	1 failure (caregiver)	Participant did not remove the transfer needle and replace with injection needle. Participant became aware of the error after the injection. Participant did not follow the IFU and did not make this error during the second scenario. Genentech added additional instructions to warn users not to inject with the transfer needle to the IFU.	Injecting with the transfer needle may cause more injection site reactions (pain and bleeding). Additionally, the participant realized their error. The Applicant has modified the IFU to address the use errors observed with this task in the study. We agree with the modifications and do not have any further recommendations to mitigate the risk for these

			errors. We find the residual risk acceptable
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3. Labeling Comprehension Evaluation

The participants for the most part were able to locate the information and comprehend the labeling to respond to the comprehension questions. Some participants were not able to locate the information in the IFU pertaining to checking the expiration dates of needle/syringe and inspecting the syringe/needle. Genentech determined that these risks are not specific to emicizumab and apply to all syringes and needles. Genentech determined that the residual risk has been evaluated to be within acceptable limits and change is not needed. We agree with this assessment.

3.2 LABELS AND LABELING

In addition to the human factors study evaluation, DMEPA reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We note (b) (4) "single dose" in carton labeling and container label, thus, we defer to Office of Pharmaceutical Quality/CMC for appropriateness of the terms and recommend consistency.

We noted several areas that could be clarified within the proposed container labels, carton labeling, instructions for use (IFU), and Prescribing Information (PI). We provide recommendations in Section 4.1 for the Prescribing Information and Instructions for Use and in Section 4.2 for container label and carton labeling.

In summary, we expect patients, caregivers, and health care professionals will be able to use Hemlibra (emicizumab) safely and effectively.

4 CONCLUSION & RECOMMENDATIONS

The HF validation study results showed failures on critical tasks. The root cause analysis and subjective feedback indicated that some additional changes to the proposed labeling are necessary to improve clarity of the product labeling which the Applicant made.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Highlights of Prescribing Information-Dosage Forms and Strengths

- i. Per USP General Chapters <7> Labeling: (b) (4)
- (b) (4) For the 30 mg/mL and 150 mg/mL (b) (4)
- (b) (4) in both Highlights and Full PI Section 3 and throughout the PI.

- ii. Per USP General Chapters <7> Labeling: [REDACTED] (b) (4)
 - iii. Add statement "See Full Prescribing Information for important preparation and administration instructions." We recommend this to ensure this important information is not missed.
2. **Full Prescribing Information (PI) Dosage and Administration: Section 2.2 (Preparation and Administration)**
- i. Consider replacing the symbol "<" with the intended meaning to prevent misinterpretation and confusion, per Draft Guidance: Container and Carton, April 2013 (lines 242-244, 479), and ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations.
 - ii. See Recommendation A.1.i and A.1.ii.
3. **Full Prescribing Information (PI) Dosage and Administration: Section 2.3 (Preparation and Administration)**
- i. We note the use of the abbreviation 'U' for 'units'. This is considered a dangerous abbreviation per the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols and Dose Designations. As part of a national campaign to avoid the use of dangerous dose designations, FDA agreed not to approve such error dose designations in the approved labeling of products. Thus, remove all instances of abbreviations such as 'U' and replace with intended meaning, 'units'.
 - ii. We recommend the unit of measure be included after each value (e.g., 2 mL) throughout the PI to prevent confusion.
4. **Full Prescribing Information (PI) Dosage Forms and Strength: Section 3**
- i. [REDACTED] (b) (4)
 - ii. [REDACTED] (b) (4)

B. Instructions for Use

1. Revise the presentation of the product name to include the proprietary name, pronunciation of proprietary name, established name, and route of administration as follows:

Instructions for Use
 Proprietary Name (pronunciation)
 (emicizumab) injection
 for subcutaneous use

2. Recommend the last bullet on *Important Information* be revised to include patient friendly language. Revise to "[REDACTED] (b) (4) ."
3. Delete the first bullet under the *Preparing the syringe for injection* as this information is already incorporated in Step 12.

4. The second bullet in *Preparing the syringe for injection* states “ (b) (4) (b) (4) ”. The third bullet in *Preparing the syringe for injection* states that the “ (b) (4) (b) (4) ”. Given the discrepancy between the time to administration, consider deleting the statement (b) (4) ”
5. The third bullet in *Preparing the syringe for injection* contains information that is stated in the first bullet of that section. Therefore, consider revising the third bullet under the *Preparing the syringe for injection* to the following: “ (b) (4) (b) (4) ”
6. Include the information of disposing all materials (i.e., vial[s], needles, etc) that are in the last bullet under *Preparing the syringe for injection* in Step 17 as well to ensure it is not overlooked.
7. Incorporate the bullets under *Important: Always keep the sharps disposal container out of reach of children* in Step 17 as all the information pertains to disposal to ensure it is not overlooked.

4.2 RECOMMENDATIONS FOR GENENTECH, INC.

We recommend the following be implemented prior to approval of this BLA:

A. Carton Labeling

1. (b) (4) (b) (4)
 Revise the strength presentations as follows:
 - i. from “ (b) (4) ” to read “30 mg/mL”;
 - ii. from “ (b) (4) ” to read “60 mg/0.4 mL”;
 - iii. from “ (b) (4) ” to read “ 105 mg/0.7 mL”;
 - iv. from “ (b) (4) ” to read “150 mg/mL”.
2. For consistency with the prescribing information, revise the storage statement from (b) (4) (b) (4) to read
“Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do Not Freeze. Do Not Shake.
 May be removed from and returned to refrigerator if necessary. If returned to refrigerator, the temperature and total combined time out of refrigeration should not exceed 30°C (86°F) and 7 days (at a temperature below 30°C [86°F]), respectively. Write the date removed from the refrigerator ___/___/___.”

Note that the “__/__/__” statement will alert the healthcare providers to write a complete date (month, day, and year) on the carton label.

3. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., 6666, 6667, and 6668), nor is using the identical product code for injectable products containing the same concentration of drug but different total volumes. If for some reason the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number or put them in bold type. For example: XXXX-**XXXX**-XX.
4. Revise the font size of the 30 mg/mL strength to be consistent with the font sizes of the other strengths.

B. Container Label

1. See Recommendations A.1 and A.3
2. Re-locate the statement “Discard Any Unused Portion” to appear below the package type term to ensure that the product is used as intended:

For Subcutaneous Use
Single Dose Vial
Discard Unused Portion

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Hemlibra that Genentech, Inc. submitted on June 23, 2017.

Table 2. Relevant Product Information for Hemlibra	
Initial Approval Date	N/A
Active Ingredient	emicizumab
Indication	For routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	<ul style="list-style-type: none"> • (b) (4) • 60 mg/0.4 mL • 105 mg/0.7 mL • (b) (4)
Dose and Frequency	3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly.
How Supplied	<p>As (b) (4) vials in the following strengths:</p> <ul style="list-style-type: none"> • (b) (4) (30 mg/mL), Sky Blue color indicator, NDC 50242-920-01 • 60 mg/0.4 mL (150 mg/mL), Purple color indicator, NDC 50242-921-01 • 105 mg/0.7 mL (150 mg/mL), Turquoise color indicator, NDC 50242-922-01 • (b) (4) (150 mg/mL), Brown color indicator, NDC 50242-923-01
Storage	<ul style="list-style-type: none"> • Store vials in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake. • Prior to administration, unopened vials (b) (4) <p>(b) (4)</p> <p>(b) (4)</p>

	(b) (4)
Container Closure	Vial: 3 mL, USP/Ph. Eur./JP Type I glass, (b) (4) colorless Stopper: (b) (4) rubber Sealing Cap: 15 mm, aluminum cap with plastic flip-off disk

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 7, 2017, we searched the L:drive and AIMS using the terms, Hemlibra to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one human factors protocol review^d, and we confirmed that our previous recommendations were considered.

^dGarrison, N. Human Factors Protocol Review for emicizumab IND 122954. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 SEP 7. RCM No.: 2016-1577.

APPENDIX C. HUMAN FACTORS STUDY

<\\cdsesub1\evsprod\bla761083\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hemophilia-a\5354-other-stud-rep\human-factors\human-factors-report.pdf>

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CASMIR I OGBONNA
10/12/2017

HINA S MEHTA
10/12/2017

MISHALE P MISTRY
10/13/2017

**REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761083

Application Type: New BLA

Drug Name(s)/Dosage Form(s): Proposed proprietary name Hemlibra (emicizumab) injection

Applicant: Genentech, Inc.

Receipt Date: June 23, 2017

Goal Date: February 23, 2018 (Targeting November 15, 2017)

1. Regulatory History and Applicant's Main Proposals

Genentech, Inc. had a pre-BLA meeting with the Agency on March 21, 2017. The first part of the rolling Original BLA submission for Genentech's BLA 761083 emicizumab was submitted and received on May 31, 2017; including the majority of Module 1, Module 2 (CMC components), Module 3, Module 4, and the OSI information in Module 5. The final components were submitted and received on June 23, 2017.

The proposed indication for BLA 761083 emicizumab (subcutaneous injection) is for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital Factor VIII deficiency) with factor VIII inhibitors. In addition, emicizumab received breakthrough designation status on September 2, 2015, under IND 122954.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

- YES** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

Selected Requirements of Prescribing Information

• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, “**HIGHLIGHTS OF PRESCRIBING INFORMATION**” must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS**”

Selected Requirements of Prescribing Information

INFECTIONS and ACUTE HEPATIC FAILURE". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement "*See full prescribing information for complete boxed warning.*" This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "*See full prescribing information for complete boxed warning.*")

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

- YES** 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment: Delete the underline under *www.fda.gov/medwatch*

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- See 17 for **PATIENT COUNSELING INFORMATION** and **FDA-approved patient labeling**
- See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**

Comment:

Revision Date in Highlights

- YES** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA C WALL
09/21/2017

PATRICIA N GARVEY
09/27/2017

CLINICAL INSPECTION SUMMARY

Date	August 23, 2017
From	Anthony Orenca M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lori Ehrlich, M.D., Ph.D. Medical Officer R. Angelo de Claro, M.D., Clinical Team Leader Laura Wall, M.Sc., Regulatory Project Manager Division of Hematology Products
BLA	761083
Applicant	Genentech
Drug	emicizumab (RO5534262)
NME	Yes
Therapeutic Classification/Status	Humanized bispecific antibody that acts as a Factor VIII–mimetic agent
Proposed Indication	Treatment of patients with hemophilia A
Consultation Request Date	June 23, 2017
Summary Goal Date	September 30, 2017
Action Goal Date	November 15, 2017
PDUFA Date	February 23, 2018 [Breakthrough-Priority review]

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Young and Kempton) were selected by the Division of Hematology Products (DHP) for inspection in support of BLA 761083. Genentech (sponsor) was also inspected. The study data derived from these clinical sites is considered to be reliable in support of the requested indication.

The preliminary regulatory classification for Drs. Young and Kempton is No Action Indicated (NAI). The preliminary regulatory classification for the inspection of Genentech is No Action Indicated (NAI).

2. BACKGROUND

Hemophilia A patients have decreased or lack circulating levels of factor VIII (FVIII). Emicizumab (RO5534262) is a humanized bispecific antibody mimicking the cofactor function of

FVIII. This product could promote the activation of FXb via FIXa, and subsequently hemostasis at the bleeding site, in patients with hemophilia A, irrespective of the presence of FVIII inhibitors.

For this BLA, DHP requests two clinical study sites, along with a sponsor inspection of Studies BH29884 and BH29992 submitted in support of this application. Dr. Young's site was the highest enrolling U.S. principal investigator for pediatric patients. Dr. Kempton's site was the highest enrolling adult patients.

Study BH29884

Study BH29884 was a randomized Phase 3 trial for patients 12 years old and older with hemophilia A with inhibitors. This was a four arm study. Patients who had been previously treated with episodic bypassing agents were enrolled in the randomized part of the trial for emicizumab prophylaxis (Arm A) versus no prophylaxis (Arm B) for 24 weeks duration. After 24 weeks, patients randomized to no prophylaxis were crossed over to emicizumab prophylaxis. Patients who were on prophylaxis with a bypassing agent at study enrollment were enrolled in Arm C and all patients were treated with emicizumab as a prophylactic agent. Arm D included patients (1) who had enrolled in a non-interventional study (BH29768) or (2) patients on prior prophylaxis who were not able to enroll in this study prior to closure of Arms A-C.

The primary efficacy objective was to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with hemophilia A with inhibitors (Arms A and B) on the basis of the number of bleeds reported over time (i.e., bleed rate). The primary endpoint included only bleeds requiring treatment. Secondary objectives included evaluation of the efficacy in reducing the number of bleeds over time compared with the patient's historical bleed rate over the last 24 weeks prior to study entry, health-related quality of life (HRQoL), and health status. Secondary endpoints included all bleeds (i.e., those treated and not treated with coagulation factors), spontaneous bleeds, joint bleeds, and target joint bleeds. Safety objectives include incidence and severity of adverse events, thromboembolic events, injection-site reactions, severe hypersensitivity events, thrombotic microangiopathy, and anti-emicizumab antibodies.

This multicenter study was conducted in 14 countries at 23 study sites including U.S., Europe, Japan, and South Korea. A total of 109 study subjects enrolled. Study BH29884 met the primary endpoint of reduction of bleeds (i.e., treated bleeds).

Study BH29992

Study BH29992 is a single-arm, ongoing trial for pediatric patients < 12 years old or 12-17 years old with weight less than 40 kg with hemophilia A with inhibitors. Patients who were either on prior episodic bypassing agent or prior prophylaxis with a bypassing agent were eligible. All patients are treated with prophylaxis with emicizumab. The clinical study report contained within the application contains analyses from the combined (first and second planned) interim analyses with a clinical data cutoff date of October 28, 2016.

The efficacy objectives of the study were to evaluate the number of bleeds over time (i.e., bleed rate), reduction in bleeds over time compared with the patient's historical bleed rate, efficacy of up-

titration, and HRQoL (or proxy HRQoL). Bleed events included treated bleeding episodes, all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds. Safety objectives included incidence and severity of adverse events, thromboembolic events, injection-site reactions, severe hypersensitivity events, thrombotic microangiopathy, and anti-emicizumab antibodies.

This study was conducted in five countries at 12 clinical study sites, including U.S., U.K., Spain, Italy, and Japan. A total of 20 study subjects enrolled. Interim results showed no treated bleeds in 18 of 19 subjects while receiving emicizumab prophylaxis.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site ## Subjects	Inspection Dates	Classification
Guy Young, M.D. Childrens Hospital Los Angeles Mail Stop 44, 4650 Sunset Boulevard Los Angeles, CA 90010	Study BH29884 Site 289318 7 Screened 7 Enrolled Study BH29992 Site 291688 4 Screened 4 Enrolled	August 14 to 17, 2017	Pending: Preliminary NAI
Christine Kempton, M.D. Winship Cancer Institute, Emory Univ. Clinic IDS 1365 Clifton Rd. NE, Bldg A, Suite 1200 Atlanta, GA 30322	Study BH29884 Site 287909 4 Screened 4 Enrolled	July 17 to 19, 2017	Pending: Preliminary NAI
Sponsor: Genentech 1 DNA Way South San Francisco, California 94080	Study BH29884 Study BH29992	July 31 to August 4, 2017	Pending: Preliminary NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Guy Young, M.D./Study BH29884 Site 289318 & Study BH29992 Site 291688

The inspection was conducted from August 14 to 17, 2017. For Study BH29884, a total of seven study patients were screened and enrolled. Seven subjects completed the study. For Study BH29992, a total of four study subjects were screened and enrolled. The study is ongoing. A complete audit of the subjects' records enrolled in both study sites was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.

2. Christine Kempton, M.D./Study BH29884 Site 287909

The inspection was conducted from July 17 to 19, 2017. A total of four study subjects were screened and enrolled. Four subjects completed the study. An audit of all the subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

Sponsor

3. Genentech

This inspection was conducted from July 31 to August 4, 2017.

The sponsor inspection included review of the following: regulatory site set up, financial disclosures, site management and monitoring, and trial master file.

Monitoring plans and visits including study site closeout were reviewed; monitoring reports indicated that the sites received adequate periodic monitoring. IRB approvals, site study protocol deviations, serious adverse events and related monitoring reports were assessed, and oversight by the sponsor appeared to be adequate. There were no under-reporting of serious adverse events.

A Form FDA 483 was not issued at the end of the inspection.

The sponsor maintained adequate oversight of the clinical trial.

{See appended electronic signature page}

Anthony Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Janice Pohlman, M.D., M.P.H., Team Leader
Good Clinical Practice Assessment Branch
Kassa Ayalew, M.D., M.P.H., Branch Chief
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
08/23/2017

JANICE K POHLMAN
08/23/2017

KASSA AYALEW
08/23/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 761083	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: proposed proprietary name Hemlibra submitted and received 6/28/17 Established/Proper Name: emicizumab Dosage Form: Liquid (b) (4) Vial Strengths: 150mg/mL (1.0, 0.7, 0.4 mL); 30mg/1.0 mL Route(s) of Administration: Subcutaneous Injection		
Applicant: Genentech, Inc. Agent for Applicant (if applicable):		
Date of Application: June 23, 2017 Date of Receipt: June 23, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: February 23, 2018	Action Goal Date (if different): November 15, 2017	
Filing Date: August 22, 2017	Date of Filing Meeting: July 24, 2017	
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .		

Type of BLA		<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)			
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>					
Review Classification:		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority			
<i>The application will be a priority review if:</i> <ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 		<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher			
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)				
<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):					
List referenced IND Number(s): 122954					
Goal Dates/Product Names/Classification Properties		YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive?		<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>					
Are the established/proper and applicant names correct in electronic archive?		<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>					

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>		

<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p>	<input type="checkbox"/>	<input type="checkbox"/>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>				
<ul style="list-style-type: none"> If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If no, include template language in the 74-day letter.</p> <p>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</p> <p>Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; <u>and</u> (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</p>	<input type="checkbox"/>	<input type="checkbox"/>		

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
NDA only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p>Forms and Certifications</p> <p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		This application has orphan designation.
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	This application has orphan designation.
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 12/05/2016

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Submitted on 6/28/17
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSL/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	COA-6/28/17, OSI clinical sites inspection-6/23/17,
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 3/21/17	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 24, 2017

BACKGROUND: Genentech, Inc. had a pre-BLA meeting with the Agency on March 21, 2017. The first part of the rolling Original BLA submission for Genentech’s BLA 761083 emicizumab was submitted and received on 5/31/17; including the majority of Module 1, Module 2 (CMC components), Module 3, Module 4, and the OSI information in Module 5. The final components were submitted and received on June 23, 2017.

The proposed indication for BLA 761083 emicizumab (subcutaneous injection) is “Treatment of patients with hemophilia A (congenital Factor VIII deficiency) with factor VIII inhibitors.” In addition, IND 122954 emicizumab received breakthrough designation status on September 2, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Laura Wall	Y
	CPMS/TL:	Theresa Carioti	Y
Cross-Discipline Team Leader (CDTL)	R. Angelo De Claro		Y
Division Director/Deputy	Ann Farrell		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Lori Ehrlich	Y
	TL:	R. Angelo De Claro	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Yuhong Chen	Y
	TL:	Stacy Shord	Y

• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Xiaofeng Wang and Jiang Liu	Y
Biostatistics	Reviewer:	Xin Gao	Y
	TL:	Yuan Li Shen	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shwu-Luan Lee	N
	TL:	Christopher Sheth	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Bazarragchaа Damdinsuren	Y
	RBPM:	Andrew Shiber	N
• Drug Substance	Reviewer:	Leslie Rivera Rosado	Y
• Drug Product	Reviewer:	Nina Brahme	Y
• Process	Reviewer:		
• Microbiology (Drug Substance and Drug Product)	Reviewer:	Max Van Tassell and Aimee Cunningham (Staff Fellow)	Y
• Facility	Reviewer:	Marion Michaelis/Zhihao Peter Qiu	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:	Haoheng Yan	Y
• Labeling (BLAs only)	Reviewer:	Vicky Borders Hemphill	N
• Other (e.g., Branch Chiefs, EA Reviewer)	Micro QAL:	Maria Candauchacon	N
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Morgan Walker	N
	TL:	Barbara Fuller	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Robert Nguyen	N
	TL:	Kathleen Davis	N
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Casmir Ogbonna	N
	TL:	Hina Mehta	Y
OSE/DRISK (REMS)	Reviewer:	Mei-Yean Chen	N
	TL:	Elizabeth Everhart	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	N
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
• Discipline	Reviewer:		
	TL:		
Other attendees	Wana Manitsitkul, OSE PM		Y
	Page Crew, OSE/DPV II		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: The application did not raise significant safety or efficacy issues.
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments: No review issues for 74-day letter.</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/> YES CMC agreed to request additional stability data for DS and DP during the review cycle and a few other items (listed in CMC meeting minutes). The comparability protocol was already submitted (with the final module). CMC will request the stability data soon. <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	None
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Dr. Richard Pazdur

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): September 13, 2017

21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Filing Meeting July 24, 2017

Applicant Orientation (AOM) and post-AOM July 24, 2017

Filing Date (Day 60) August 22, 2017

Mid-Cycle Meeting (MCM) September 13, 2017

Labeling Meeting #1 September 21, 2017

Mid-Cycle communication SPON T-CON September 28, 2017

Labeling Meeting #2 September 28, 2017

Combined Labeling Meeting #3 and Wrap-Up Meeting October 5, 2017

Labeling Meeting #4 October 11, 2017

INT MTG/Pre-MTG for Late Cycle MTG and Labeling MTG #5 October 17, 2017

SPON MTG Late-Cycle October 26, 2017

Labeling Meeting #6 (Review Applicant Response) October 31, 2017

Labeling Meeting #7 (Review Applicant Response) November 7, 2017

Issue Action Letter: Action Goal Date November 15, 2017

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review</p>

ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)

<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA C WALL
08/14/2017

MARA B MILLER
08/14/2017