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RESEARCH**

APPLICATION NUMBER:

125522Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125522
Product Name: Repatha (evolocumab)

PMR #1 Description: Conduct an efficacy and safety study evaluating Repatha (evolocumab) in patients with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less than 18 years. The study will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study (Part A) followed by an 18-month open-label extension in patients 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C \geq 130 mg/dL (Part B).

PMR Schedule Milestones:	Final Protocol Submission (Part A):	<u>December 2015</u>
	Final Protocol Submission (Part B):	<u>December 2015</u>
	Study Completion (Part A):	<u>March 2018</u>
	Study Completion (Part B):	<u>September 2019</u>
	Final Report Submission (Parts A and B):	<u>April 2020</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Repatha is ready for approval for use in adults; however, pediatric studies had been deferred until adequate safety data were available.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to establish the pharmacokinetics of Repatha in the pediatric population ages 10 to < 18 to determine appropriate dosing, and to establish the safety and efficacy of Repatha in that same population.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals 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?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study followed by an 18-month open-label extension in patients 10 to <18 years with HeFH on stable lipid-modifying therapy with LDL-C \geq 130 mg/dL.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

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

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125522
Product Name: Repatha (evolocumab)

PMR #2 Description: Conduct a prospective observational study of pregnant women exposed to Repatha (evolocumab) to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to evolocumab and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression. The study should have validated/adjudicated outcomes, a comparator group, be powered to detect the outcomes of interest, and include the justification for the proposed detectable differences in incidence rates.

PMR Schedule Milestones:	Final Protocol Submission:	<u>August 2016</u>
	Interim Report Submissions	October 2017
		October 2018
		October 2019
		October 2020
		October 2021
		October 2022
		October 2023
		October 2024
		October 2025
		October 2026
		October 2027
	October 2028	
October 2029		
Study Completion:	<u>October 2030</u>	
Final Report Submission:	<u>April 2031</u>	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A long-term study of women exposed to Repatha during pregnancy is needed; this is only feasible in the post-approval setting.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In studies done with Praluent/alirocumab, which is in the same class as Repatha, it was found that in cynomolgus monkeys, suppression of the humoral immune response to keyhole limpet hemocyanin (KLH) antigen was observed in infant monkeys at 4 to 6 months of age when alirocumab was dosed during organogenesis to parturition at 15 mg/kg/week and 75 mg/kg/week by the subcutaneous route, corresponding to 13- and 81-fold the human exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC. The lowest dose tested in the monkey resulted in humoral immune suppression; therefore it is unknown if this effect would be observed at clinical exposure. No study designed to challenge the immune system of infant monkeys was conducted. No additional embryo-fetal, prenatal or postnatal effects were observed in infant monkeys, and no maternal effects were observed, when alirocumab was dosed at up to 75 mg/kg/week by the subcutaneous route, corresponding to maternal exposure of 81-fold the exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC. A similar study was not performed with Repatha/evolocumab, but the concern is that this may be a class effect.

Given the nonclinical findings described above, there is concern for the possibility of adverse events in infants such as poor vaccine response and increased infections.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals 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?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A prospective observational study of pregnant women exposed to Repatha to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to Repatha and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression. The study should have validated/adjudicated outcomes, a comparator group, be powered to detect the outcomes of interest, and include the justification for the proposed detectable differences in incidence rates.

Required

Observational pharmacoepidemiologic study

Registry studies

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

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

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125522
Product Name: Repatha (evolocumab)

PMR #3 Description: Conduct a large, randomized, controlled, long-term trial in which the incidence and severity of new-onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity, and adverse events potentially related to demyelination with Repatha (evolocumab) will be evaluated.

PMR Schedule Milestones:	Final Protocol Submission:	<u>January 2016</u>
	Trial Completion:	<u>September 2017</u>
	Final Report Submission:	<u>June 2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

To assess the potential safety issues of new-onset diabetes mellitus, injection site reactions, hypersensitivity, immunogenicity, and adverse events potentially related to demyelination, a large long-term trial is needed. This is only feasible to conduct post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to evaluate signals of new-onset diabetes mellitus, injection site reactions, and hypersensitivity/allergic reactions.

An integrated analysis of phase 2 and phase 3 trials of Repatha was performed to assess for new onset diabetes mellitus. Using a definition that included adverse events consistent with diabetes, initiation of anti-diabetic medication or at least two consecutive post-baseline fasting blood glucose (FBG) measurements ≥ 126 mg/dL, in the group with impaired fasting glucose (IFG), defined as $100 \leq \text{FBG} < 126$ mg/dL, there was an increase in post baseline new onset diabetes in the Repatha group (2.6% Placebo vs 1.9% Any Control vs 3.1% Repatha). For the majority of patients treated with Repatha, glucose control remained stable. It is unknown if these findings represent a true risk for new onset diabetes with Repatha treatment.

Local injection site reactions including erythema/redness, itching, swelling, and pain/tenderness were reported more frequently in patients treated with Repatha (b) (4) (%) versus placebo (b) (4) (%).

Hypersensitivity/allergic reactions (e.g., pruritus, rash, urticaria) were reported more frequently in patients treated with Repatha (3.2%) versus placebo (2.4%).

In a pool of placebo- and active-controlled clinical trials, 0.1% of patients treated with at least one dose of Repatha tested positive for binding antibody development. The 7 patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies; none of the patients tested positive for neutralizing antibodies. There was no evidence that the presence of anti-evolocumab binding antibodies impacted the pharmacokinetic profile, clinical response, or safety of Repatha.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals 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?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A large, randomized, controlled, long-term trial. The Sponsor intends to use their ongoing CVOT to fulfill this PMR.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

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

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # BLA 125522
Product Name: Repatha (evolocumab)

PMR #4 Description: Conduct a randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with Repatha (evolocumab) treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect.

PMR Schedule Milestones:	Final Protocol Submission:	<u>November 2015</u>
	Trial Completion:	<u>September 2017</u>
	Final Report Submission:	<u>June 2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The concern described below is theoretical, and may not be relevant to PCSK9 inhibitors as (1) the molecule is generally not expected to cross the blood-brain barrier, and (2) evidence suggests that the brain generates its own cholesterol. Neurocognitive events were similar between Repatha (0.15%) and placebo (0.13%).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this PMR is to evaluate the theoretical concern for neurocognitive effects. There have been rare postmarketing reports of cognitive impairment (e.g., memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use (class labeling), which led to the concern regarding potential neurocognitive effects associated with low LDL cholesterol.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals 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?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with evolocumab treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

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

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs)

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Accumulation and statistical analysis of additional DS stability data at the (b)₍₄₎ °C condition.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs only)

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Study could be either a de-novo validation of the assay or assay transfer qualification study comparing the assay implemented at ATO with the assay implemented at either (b) (4) or AML.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs only)

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Accumulation of additional datapoints and statistical analysis of data acquired following manufacture of additional lots

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs only)

2. Describe the particular review issue and the goal of the study.

(b) (4)

The acceptance criteria being approved were developed based on data available in the BLA. Sponsor claimed they needed additional data to enable a robust statistically based assessment of the limit. Increased manufacturing and testing experience gained post licensure can facilitate improved specifications. Updating the acceptance criteria would be done to ensure continued control through the product lifecycle, including anticipated future manufacturing changes.

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Accumulation of additional datapoints and statistical analysis of data acquired following manufacture of additional lots.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs only)

3. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Statistical analysis of release data acquired following manufacture of additional lots.

4. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- 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.*

(signature line for BLAs only)

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/s/

JENNIFER R PIPPINS
08/27/2015



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Addendum to Maternal Health Review

Date: August 6, 2015

From: Christos Mastroyannis, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Division Director,
Division of Pediatric and Maternal Health

To: The Division of Metabolism and Endocrinology Products (DMEP)

Drug: Repatha (evolocumab)

BLA: 125522

Subject: How to investigate further a potential theoretical risk of humoral immune suppression in infants born to mothers who used Repatha during pregnancy

Applicant Amgen, Inc.

Purpose

This document discusses the postmarketing requirement (PMR) for Repatha and serves as an addendum to the Maternal Health consult review written by C. Mastroyannis, MD, dated July 2, 2015.

Introduction

On August 27, 2014, Amgen submitted BLA 125522 for REPATHA (evolocumab) subcutaneous injection, to be used for the treatment of adult patients with hyperlipidemia or mixed dyslipidemia and in pediatric patients 12 years of age and older with homozygous familial hypercholesterolemia (HoFH). A similar PCSK9 inhibitor antibody, Praluent (alirocumab), BLA 125559, was approved on July 24, 2015. During the product development of Praluent, a T-cell Dependent Antibody Response (TDAR) study in offspring of cynomolgus monkeys who were administered alicumab during pregnancy demonstrated a signal of serious risk of humoral immune suppression (IgG). Amgen failed to perform a TDAR study with the drug product Repatha. Such a study is a requirement per the ICH S8 Guidance for Industry Immunotoxicity Studies for Human Pharmaceuticals. The approval letter for Praluent asks for a PMR to further study the effects of Praluent during pregnancy and specifically to address the potential theoretical risk of humoral immune suppression in the offsprings of pregnant women who received Praluent during their pregnancy.

Product Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secretory serine protease that homeostatically regulates the amount of plasma LDL-C by interacting with the LDL receptor (LDL-R). After binding to LDL-R and internalization, PCSK9 directs the LDL-R to lysosomal degradation, inhibiting its recycling to the hepatocyte surface and thus catabolism of plasma LDL-C¹. LDL-R is the primary receptor that clears circulating LDL, therefore, the decrease in LDL-R levels by PCSK9 results in higher blood levels of LDL-C. REPATHA is a human monoclonal IgG2 antibody. It belongs to the group of PCSK9 inhibitor antibodies. REPATHA binds selectively and with high affinity to PCSK9 and inhibits circulating PCSK9 from binding to the LDL-R, on the liver cell surface, thus preventing PCSK9-mediated LDL-R degradation. This action permits LDL-R to recycle back to the liver cell surface. Increasing liver LDL-R levels result in associated reductions in serum LDL-C.

Discussion

DPMH has determined that the signal of humoral immune suppression, demonstrated in the offspring of pregnant cynomolgus monkeys administered alicumab, identifies a potential safety concern for neonates and infants when a pregnant woman is administered Praluent or Repatha (PCSK9 inhibitor antibodies). Further assessment of this potential safety concern is necessary to monitor for adverse neonatal and infant outcomes (i.e., recurrent infections with encapsulated bacteria, life-threatening enterovirus infections, failure to respond to appropriate antibiotic therapy). In addition, due to the lack of adequate safety information on the use of Praluent and Repatha in pregnant women, assessment of pregnancy outcomes and embryo-fetal growth and development are recommended. Based on the finding of humoral immune suppression in infant monkeys with Praluent and a potential theoretical serious risk for human infants who were

¹ Santos RD and Watts GF. Familial hypercholesterolemia: PCSK9 inhibitors are coming. *The Lancet*, 2015;385(9965):331-340

exposed to Repatha in utero, DPMH recommends further evaluation of Repatha administration during pregnancy.

Amgen, in the European Union Risk Management Plan, has proposed a multinational observational study (Study 20150162) to evaluate outcomes of pregnancy in females diagnosed with familial hypercholesterolemia (FH), exposed to Repatha during pregnancy. This study, (b) (4) represents an enhanced pharmacovigilance program similar to DPMH's recommendation.



DPMH Recommendation

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

DPMH recommends the applicant conduct a prospective observational study of pregnant women exposed to Repatha. The study may be conducted as an enhanced pregnancy pharmacovigilance program, similar to Amgen's proposed prospective observational study. The study should be conducted to evaluate adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant outcomes related to humoral immune suppression. Further discussions about the specific study design may be decided after the approval of Repatha. DPMH welcomes the opportunity to perform a thorough review of the final protocol for the PMR study when it is submitted by Amgen.

The reader is referred to the approval letter for the final negotiated post-marketing requirement.

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/s/

TAMARA N JOHNSON
08/18/2015

LYNNE P YAO
08/25/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, and Ophthalmic Device Branch

DATE: August 13, 2015

TO: Lakshmi Narasimhan, OMPT/CDER/OPQ/OPF/DMA/MABIV
Lakshmi.Narasimhan@fda.hhs.gov
Pat Hughes, OMPT/CDER/OPQ/OPF/DMA/MABIV
Office of combination products at combination@fda.gov

RPM: Kati Johnson

Through: LT Viky Verna, Chief, REGO, DMQ, OC, CDRH WO-66, Room 2628

Viky Verna - A
Digitally signed by Viky Verna - A
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ou=FDA, ou=People, cn=Viky Verna - A,
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Date: 2015.08.13 15:13:10 -04'00'

From: Crystal Lewis, REGO DMQ, OC, CDRH WO-66, Room 2628

Applicant: Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

FEI# 1000110364

Application # BLA125522

Consult # ICC#1400676

Product Name: Evolocumab

Consult CDRH and the Office of Compliance received a consult for BLA STN 125522/0 (Evolocumab) to assess the suitability of the pre filled syringe and pen injector and the need for inspection of the

Instructions: following sites. CDER provided the list of possible inspection sites.

Inspection Needed: No Recommendation Date: 07/15/2015

Site: Amgen, Inc. (Amgen Louisville Distribution Center or LDC)

12000 Plantside Drive Louisville, KY 40299 USA

FEI: 3003750095

Documentation Review: No additional information required

Final Recommendation: Approval

PRODUCT DESCRIPTION

Evolocumab is a full-length human monoclonal antibody produced in Chinese hamster ovary (CHO) cells. Evolocumab specifically binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9) and prevents its interaction with the low density lipoprotein receptor (LDLR). LDLR recycling is required in the maintenance of cellular and whole body cholesterol homeostasis by regulating plasma low density lipoprotein cholesterol (LDL-C) levels.

Evolocumab is a biologic and drug product used to facilitate the lowering of serum LDL-C by increasing the cell surface level of the LDLR. Evolocumab drug product is supplied as a sterile, preservative-free solution for administration by subcutaneous (SC) injection. The firm supplies the drug product in the following dosages:

(b) (4)

- 140 mg/mL prefilled syringe (PFS)
- 140 mg/mL prefilled autoinjector/pen (AI/pen)

(b) (4)

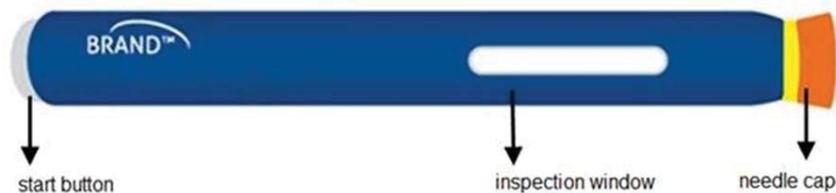
Each dose is intended to provide a single use, fixed dose for subcutaneous injection by a health care professional, a caregiver or patient. Administration may be either in the clinic or a non-clinical environment. The formulations (b) (4) consist of a 1.0 mL deliverable volume (140 mg evolocumab) in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The Evolocumab drug product manufacturing process consists of (b) (4)

(b) (4)

Assembly of the Prefilled AI/Pen



Autoinjector/Pen (AI/Pen)



REGULATORY HISTORY

The following firms were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Amgen Manufacturing Ltd (AML)
Road 31, Kilometer 24.6
Juncos, Puerto Rico 00777 USA

An analysis of the firm's inspection history over the past 2 years revealed a device inspection was conducted from 01/12/2015 to 01/23/2015, and objectionable conditions were identified. However, a 483 was not issued and the inspection was classified VAI. Since there was a recent medical device inspection which was classified as VAI, a pre-approval inspection is not required for this firm.

2. Amgen Inc. (referred to as Amgen Louisville Distribution Center or LDC)
12000 Plantside Drive
Louisville, KY 40299 USA

An analysis of the firm's inspection history revealed an initial inspection was conducted of a drug storage and distribution warehouse. A drug inspection was conducted from 01/05/2006 to 01/06/2006, no deficiencies were found and the inspection was classified NAI. No apparent issues related to 21 CFR part 820 were found. The firm's LDC site does not perform activities for the manufacture and assembly of the prefilled autoinjector

and pen. The firm only performs drug manufacturing activities. Therefore, an inspection is not required for this firm.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

The firm identified Amgen, Inc. as the firm who is ultimately responsible for the overall combination product. The firm explained how all firms involved in the manufacturing of the combination product will be controlled to ensure it is designed and produced in accordance with the applicable Quality Systems requirements. Amgen also describes how the quality policy will be implemented and maintained at all levels of the organization.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm details the design controls in the Design Device Validation document which includes standard operating procedures (SOP) that apply to Amgen's combination products including medical devices. The firm's document covers procedures for design validation activities for devices that are designed and manufactured by Amgen, a partner, or contract-manufacturer, and are a part of an Amgen Combination Product. Amgen uses this SOP for sites that perform design validation activities and functions for software and medical device accessories.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

Amgen states it has qualified and instituted quality agreements with the component/sub-assembly suppliers and design partners for the device constituent parts of the Evolocumab combination products with sub-contractors included within the agreements (Table 2). The firm's purchasing controls are provided in the document entitled Supplier Related Raw Material Nonconformance and Issue Management Process. Amgen details its controls through requirements for identifying, communicating and managing raw materials and component related non-conformances (NC) and the investigations at Amgen manufacturing locations. This SOP covers NC initiation, management, supplier response evaluation, CAPA, supplier recalls and notification of quality concerns, Amgen contract manufacturing activities, sample collection, site determination of local scope of impact, network triage and

supplier response evaluation and raw material lot number information.

Table 2. Supplier/Design Partner Quality Management System (QMS) Documents and Device Master Files (MAFs)

Device	Supplier/Design Partner (MAF Submitter)	Facility QMS Documents	MAF Reference Number	Letter of Authorization (LOA)
				(b) (4)

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

Amgen details its CAPA procedure in the operating standard for corrective and preventive action. This document is the firm’s operating standard and is used to describe the process requirements for CAPA. The firm states this operating standard is applicable to all Amgen sites or functions performing GMP production, testing storage, and distribution of drug substances, drug products and combination products.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls

The firm’s submission identifies Production and Process controls in the document entitled “Description of Manufacturing Process and Process Controls”. The 140mg/ml drug product manufacturing processes identified include a process flow diagram with operational parameters. These parameters include materials added, process conditions, process steps and in-process testing (Figure 1). The firm’s manufacturing processes includes [REDACTED] (b) (4),

(b) (4)

The firm also provided a validation plan for manufacturing equipment and environmental controls.

Figure 1. 140 mg/mL Drug Product Manufacturing Process Flow Chart

(b) (4)



Production Flow

Amgen provided a flow chart of the manufacturing process for the Evolocumab combination product. The firm described procedures for the prefilled AI/Pen including assembly, labeling, and packaging (Figure 1 below).

Figure 1. 140 mg/mL Prefilled AI/Pen Assembly, Labeling and Packaging Process Flow Diagram



Acceptance Activities

The firm provided information regarding acceptance activities of the device. The testing details the acceptance activities of the device as they are processed for the manufacturing of the final combination product. Specifically, the firm provided acceptance criteria as part of the design verification for AMG 145 PFS which included three lots of the device. See the tables below.

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Table 7. Stress Cracking Data for PCS-001590

Lot #	Force (N)	Acceptance Criteria
3156311	(b) (4)	
3081152		
3080414		

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality System requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The Office of Compliance (OC) at CDRH has completed the evaluation of application BLA125522. Based on the information provided, CDRH/OC recommends approval of application Evolocumab BLA125522.

**Crystal
Lewis -S**  Digitally signed by Crystal Lewis -S
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Crystal Lewis

Prepared: CLewis: 07/21/15

Reviewed: VVerna 7/22/2015; 8/4/2015; 8/6/2015; 8/13/2015

CTS No.: ICC1400676

BLA125522

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/s/

KATI JOHNSON
08/20/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing & Quality
Respiratory, ENT, General Hospital, and Ophthalmic Device Branch

DATE: August 5, 2015

TO: Lakshmi Narasimhan, OMPT/CDER/OPQ/OPF/DMA/MABIV
Lakshmi.Narasimhan@fda.hhs.gov
Pat Hughes, OMPT/CDER/OPQ/OPF/DMA/MABIV
Office of combination products at combination@fda.gov

RPM: Kati Johnson

Through: LT Viky Verna, Chief, REGO, DMQ, OC, CDRH WO-66, Room 2628

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Date: 2015.08.06 10:14:18 -04'00'

From: Crystal Lewis, REGO DMQ, OC, CDRH WO-66, Room 2628

Applicant: Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

FEI# 1000110364

Application # BLA125522

Consult # ICC#1400676

Product Name: Evolocumab

Consult CDRH and the Office of Compliance received a consult for BLA STN 125522/0 (Evolocumab) to assess the suitability of the pre filled syringe and pen injector and the need for inspection of the following sites. CDER provided the list of possible inspection sites.

Instructions:

Inspection Needed: No Recommendation Date: 07/15/2015

Site: Amgen, Inc. (Amgen Louisville Distribution Center or LDC)
12000 Plantside Drive Louisville, KY 40299 USA

FEI: 3003750095

Documentation Review: Additional information required

Final Recommendation: **DELAYED** – Please find details recommendation justification in the Recommendation Section.

PRODUCT DESCRIPTION

Evolocumab is a full-length human monoclonal antibody produced in Chinese hamster ovary (CHO) cells. Evolocumab specifically binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9) and prevents its interaction with the low density lipoprotein receptor (LDLR). LDLR recycling is required in the maintenance of cellular and whole body cholesterol homeostasis by regulating plasma low density lipoprotein cholesterol (LDL-C) levels.

Evolocumab is a biologic and drug product used to facilitate the lowering of serum LDL-C by increasing the cell surface level of the LDLR. Evolocumab drug product is supplied as a sterile, preservative-free solution for administration by subcutaneous (SC) injection. The firm supplies the drug product in the following dosages:

(b) (4)

- 140 mg/mL prefilled syringe (PFS)
- 140 mg/mL prefilled autoinjector/pen (AI/pen)

(b) (4)

Each dose is intended to provide a single use, fixed dose for subcutaneous injection by a health care professional, a caregiver or patient. Administration may be either in the clinic or a non-clinical environment. The formulations (b) (4)

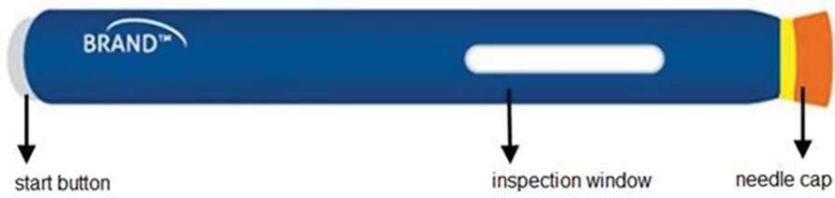
(b) (4) of a 1.0 mL deliverable volume (140 mg evolocumab) in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The Evolocumab drug product manufacturing process consists of (b) (4)

(b) (4)

Assembly of the Prefilled AI/Pen



Autoinjector/Pen (AI/Pen)



REGULATORY HISTORY

The following firms were identified as being subject to applicable Quality System Requirements under 21 CFR part 820:

1. Amgen Manufacturing Ltd (AML)
Road 31, Kilometer 24.6
Juncos, Puerto Rico 00777 USA

An analysis of the firm's inspection history over the past 2 years revealed a device inspection was conducted from 01/12/2015 to 01/23/2015, and objectionable conditions were identified. However, a 483 was not issued and the inspection was classified VAI. Since there was a recent medical device inspection which was classified as VAI, a pre-approval inspection is not required for this firm.

2. Amgen Inc. (referred to as Amgen Louisville Distribution Center or LDC)
12000 Plantside Drive
Louisville, KY 40299 USA

An analysis of the firm's inspection history revealed an initial inspection was conducted of a drug storage and distribution warehouse. A drug inspection was conducted from 01/05/2006 to 01/06/2006, no deficiencies were found and the inspection was classified NAI. No apparent issues related to 21 CFR part 820 were found. The firm's LDC site does not perform activities for the manufacture and assembly of the prefilled autoinjector and pen. The firm only performs drug manufacturing activities. Therefore, an inspection is not required for this firm.

DOCUMENTATION REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

Management Control, 21 CFR 820.20

Amgen Inc. did not identify the name of the firm who is ultimately responsible for the overall combination product. The firm did not explain how it controls all firms involved in the manufacturing to ensure it is designed and produced in accordance with the applicable Quality Systems requirements. There also does not appear to be any description of how the most responsible firm will ensure that the quality policy is implemented and maintained at all levels of the organization.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30

The firm details the design controls in the Design Device Validation document which includes standard operating procedures (SOP) that apply to Amgen's combination products including medical devices. The firm's document covers procedures for design validation activities for devices that are designed and manufactured by Amgen, a partner, or contract-manufacturer, and are a part of an Amgen Combination Product. Amgen uses this SOP for sites that perform design validation activities and functions for software and medical device accessories.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.30.

Purchasing Controls, 21 CFR 820.50

The firm's purchasing controls are provided in the document entitled Supplier Related Raw Material Nonconformance and Issue Management Process. Amgen details its controls through requirements for identifying, communicating and managing raw materials and component related non-conformances (NC) and the investigations at Amgen manufacturing locations. This SOP covers NC initiation, management, supplier response evaluation, CAPA, supplier recalls and notification of quality concerns, Amgen contract manufacturing activities, sample collection, site determination of local scope of impact, network triage and supplier response evaluation and raw material lot number information.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.50.

Corrective and Preventive Action (CAPA), 21 CFR 820.100

Amgen details its CAPA procedure in the operating standard for corrective and preventive action. This document is the firm's operating standard and is used to describe the process requirements for CAPA. The firm states this operating standard is applicable to all Amgen sites or functions performing GMP production, testing storage, and distribution of drug substances, drug products and combination products.

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.100.

Installation, 21 CFR 820.170

Installation is not required for this combination product.

Servicing, 21 CFR 820.200

Servicing is not required for this combination product.

MANUFACTURING

Production and Process Controls

The firm's submission identifies Production and Process controls in the document entitled "AMG 145 Pre Filled Syringe Packaging Distribution, and Device Functional Testing Verification Report". However, the firm did not provide information about how it will control the manufacturing process. The firm's submission did not include a validation plan for manufacturing equipment or environmental controls.

Production Flow

Amgen did not provide a flow chart of the manufacturing process for the Evolocumab combination product.

Acceptance Activities

The firm did not provide information regarding testing of incoming, in process and final acceptance activities of the device. The testing should detail these acceptance activities of the device as they are processed for the manufacturing of the final combination product.

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

Deficiencies to be conveyed to the applicant

The following deficiencies have been identified while doing the documentation review of the application for Evolocumab, BLA 125522, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. Per the application, several firms are involved in the manufacturing of finished combination product. However, your firm did not describe the organizational structure (i.e. organization structure chart) and explain how it controls all levels of the structure (i.e. agreements). Please provide a complete summary that adequately addresses the requirements of 21 CFR 820.20, Management Control.
2. Please provide a summary describing the controls in place to monitor the manufacturing activities (i.e. personnel, environmental controls, equipment validation etc...) for the combination product. Please provide a flow chart of the manufacturing process for the Evolocumab combination product.

3. Please describe the acceptance activities planned as part of the manufacturing to ensure that products manufactured and distributed are within specifications. The acceptance activities should include inspections, tests, or other verification activities.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of application BLA125522 and has the following recommendations:

The approvability of application for Evolocumab-BLA125522 should be delayed for the following reason:

- Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

**Crystal
Lewis -S**

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Crystal Lewis

Prepared: CLewis: 07/21/15

Reviewed: VVerna 7/22/2015; 8/4/2015; 8/6/2015

CTS No.: ICC1400676

BLA125522

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Crystal Lewis

CSO,

REGO

DMQ

Office of Compliance, WO66 RM 2628

Phone: 301-796-6116

Secondary Contacts (if Primary is unavailable and a timely answer is required)

Viky Verna

Acting Chief

REGO

DMQ

Office of Compliance, WO66 RM 2628

Phone: 301-796- 2909

**THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM
DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL
INFORMATION**

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/s/

KATI JOHNSON

08/20/2015

OND PM archiving CDRH Compliance review #1

**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: August 13, 2015

To: Jean-Marc Guettier, M.D., Director
Division of Metabolism and Endocrinology Products (DMEP)

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

Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Ankur Kalola, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): REPATHA (evolocumab)

Dosage Form and Route: Solution for Subcutaneous Injection

Application Type/Number: BLA 125522

Applicant: Amgen, Inc.

1 INTRODUCTION

On August 27, 2014, Amgen submitted, for the Agency's review, an original Biologics License Application (BLA) for evolocumab. The proposed tradename of REPATHA was approved on September 26, 2014. The Applicant proposes that REPATHA be indicated for long-term treatment of patients with primary hyperlipidemia, mixed dyslipidemia, as well as homozygous familial hypercholesterolemia (HoFH).

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 DMEP on September 10, 2014, and September 10 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for REPATHA (evolocumab) solution for subcutaneous injection.

2 MATERIAL REVIEWED

- Draft REPATHA (evolocumab) solution for subcutaneous injection PPI and IFUs received on August 24, 2014, and received by DMPP on August 4, 2015.
- Draft REPATHA (evolocumab) solution for subcutaneous injection PPI and IFUs received on August 24, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on August 4, 2015.
- Draft REPATHA (evolocumab) solution for subcutaneous injection Prescribing Information (PI) received on August 24, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on August 3, 2015.
- Draft REPATHA (evolocumab) solution for subcutaneous injection Prescribing Information (PI) received on August 24, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on August 3, 2015.
- Approved PRALUENT (alirocumab) solution for subcutaneous injection comparator labeling dated July 24, 2015.

3 REVIEW METHODS

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 APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI and IFUs documents using the Arial font, size 10.

In our review of the PPI and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our review of the PPI and IFUs 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 PPI and IFUs.

Please let us know if you have any questions.

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SHARON W WILLIAMS
08/13/2015

ANKUR S KALOLA
08/13/2015

MELISSA I HULETT
08/13/2015

LASHAWN M GRIFFITHS
08/13/2015

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

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

Memorandum

Date: August 11, 2015

To: Kati Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

From: Ankur Kalola, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Consult Request

BLA 125522 REPATHA (evolocumab) injection, for subcutaneous use

On September 10, 2014, OPDP received a consult request from DMEP to review the proposed draft Prescribing Information (PI), Patient Information (PPI), and Instructions for Use (IFU) for Repatha. OPDP's comments on the proposed draft PI are based on the version sent via email by Kati Johnson on August 11, 2015 and are provided below.

Additionally, OPDP will work collaboratively with DMPP to provide comments on the PPI and IFU under separate cover.

Thank you for the opportunity to comment on these materials. If you have any questions, please contact Ankur Kalola at 301-796-4530 or Ankur.Kalola@fda.hhs.gov.

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/s/

ANKUR S KALOLA
08/11/2015



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 15, 2015

To: Jean-Marc Guettier, M.D., Director
Division of Metabolism and Endocrinology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Jovita Randall-Thompson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: Repatha injection, BLA 125522
Generic Name (Trade Name): Evolocumab (Rapatha)
Dosages: 140 mg every 2 weeks and 420 mg once a month
Formulations: A prefilled syringe (PFS) and autoinjector/pen (AI/pen) containing 140 mg of evolocumab; 140 mg/ml
Routes: subcutaneous
Indication(s): Treatment for adult hyperlipidemia and mixed dyslipidemia and adult and adolescence homozygous familial hypercholesterolemia (HoFH)
Sponsor: Amgen Inc.

Materials Reviewed:

- BLA 125522, submission date August, 27, 2014
- 3.2.P.1 – Description and Composition
- 3.2.S.1.3 – General Properties
- 3.2.S.1.2 – Structure
- Phase 1 Study Reports 20110168, 20120133, 20120136, 20120135, 20080397, 20110121, and 20120341

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I. Summary

1. Background

This memorandum responds to a consult request dated 01/05/2015 from the Division of Metabolism and Endocrinology Products (DMEP) regarding evolocumab, trade name Repatha (BLA 125522).

Evolocumab is a proprotein convertase subtilisin/kexin (PCSK) antibody under development by Amgen Inc. It is being evaluated as a lipid-lowering therapy.

Evolocumab is a human monoclonal immunoglobulin IgG2 that binds selectively to PCSK type 9 (PCSK9). When bound to PCSK9, evolocumab inhibits PCSKS from binding to the low-density lipoprotein receptor (LDLR) located on the surface of hepatic cells. This in turn leads to increased LDLR expression and subsequent decreased circulation concentration of low-density lipoprotein cholesterol (LDL-C). According to the Sponsor, LDL-C is a validated surrogate endpoint for cardiovascular risk reduction.

Evolocumab is not a scheduled substance under the Controlled Substances Act (CSA). The Sponsor states in the BLA that evolocumab is not chemically or pharmacologically similar to a known drug of abuse, does not produce psychoactive effects, is unlikely to cross the blood brain barrier and its binding to and actions of PCSK9 do not affect the central nervous system (CNS) or produce neurological processes. As a result of this, the Sponsor has not performed an abuse potential assessment on evolocumab.

2. Conclusions

1. CSS conducted a review of the adverse events (AEs) collected during Phase 1 trials. No abuse related AEs were reported with evolocumab. Dizziness was reported, but not accompanied by any AEs typically associated abuse (i.e., sedation, euphoric or elevated mood), thus alone it is of low significance and considered not a signal of abuse in this case.
2. Based on evolocumab's AE profile, and subject to completion of the Agency's safety review, we agree with the Sponsor that an abuse assessment of evolocumab is not needed.
3. There is no requirement under the Controlled Substances Act (CSA, Title 21 United States Code (U.S.C.)) that mandates a formal request for a waiver of the abuse liability assessment/abuse studies for biologic drugs, particularly in the case of BLAs submitted by Sponsors.

4. Sponsors should include in BLAs information supporting their position on whether the biologic drug has or does not have an abuse potential and information supporting a position on why an abuse assessment is not needed for the drug (as Amgen Inc. has done for evolocumab/Rapatha). The Sponsor's explanation should focus on the lack of CNS or psychoactive effects (e.g., euphoria, hallucinations, or changes in mood) produced by the biologic. See 21 CFR 314.50(d)(5)(vii).
5. CSS is responsible for assessing information submitted by the Sponsor that relates to a drug's potential for abuse.

II. Discussion

According to the Sponsor, evolocumab was evaluated for 2 lipid-lowering indications in 6801 subjects, with a total exposure of 6388 patient-years. It is intended for long-term use. The Sponsor is developing evolocumab for two indications:

1. For the treatment of adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia. Given 140 mg by subcutaneous (SC) injection every 2 weeks (Q2W) and 420 mg by SC injection every month (QM).
2. In adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH). HoFH is considered a rare disease (approximately 1:1,000,000 individuals). The doses evaluated in HoFH were 420 mg SC every month and 420 mg SC every 2 weeks.

Evolocumab binds selectively and with high affinity to human proprotein convertase subtilisin/kexin type 9 (PCSK9) and inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of low-density lipoprotein cholesterol (LDL-C).

The Sponsor states that LDL-C is a validated surrogate endpoint for cardiovascular risk reduction. Inhibition of PCSK9 by evolocumab additionally leads to reductions in several types of cholesterol, including total cholesterol, apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglycerides, lipoprotein(a), total cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio, and ApoB/apolipoprotein A1 (ApoA1) ratio and increases in HDL-C and ApoA1, all of which have been shown to correlate with cardiovascular risk.

1. Chemistry

Evolocumab (formerly known as AMG 145) chemical name is anti-PCSK9 monoclonal antibody. ^{(b) (4)}



Evolocumab is a human monoclonal antibody of the immunoglobulin G2 (IgG2) subclass consisting of 2 heavy chains and 2 light chains of the lambda subclass. (b) (4)

The prefilled autoinjector/pen and the prefilled syringe are included in the current application and are proposed as self-administration products.

The autoinjector/pen (AI/pen) is a prefilled, single-use, disposable, handheld, mechanical (spring-based) injection device that is provided ready-to-use, pre-assembled with a prefilled glass syringe containing a sterile, preservative-free solution of drug product. The AI/pen is used for subcutaneous administration of a fixed dose of 1.0 ml of 140 mg/ml evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0.

The prefilled syringe (PFS) (with no autoinjector) contains a 1 ml syringe with 1.0 ml deliverable volume of 140 mg/ml evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0. The primary container closure consists of a 1 ml Type I glass syringe with a staked-in-place stainless steel needle covered with an (b) (4) needle shield and a (b) (4) plunger-stopper (b) (4). The (b) (4) needle shield is made from (b) (4).

Both the AI/pen and PFS contents include: evolocumab (140 mg, active ingredient), proline (25 mg, (b) (4) acetic acid (1.2 mg, (b) (4) polysorbate 80 (0.10 mg, (b) (4) sodium hydroxide (b) (4) and water (b) (4).

Based on SC administration, the median Tmax is reported at 48 hours at a dose of 21 mg and up to 168 hours at a dose of 420 mg. The Cmax and AUC0-inf point estimates of the slope (90% confidence interval) were 1.23 (1.06, 1.40) and 1.63 (1.29, 1.96), respectively, over a 20-fold range of doses (21 mg to 420 mg), indicating that evolocumab serum concentrations increased in a greater-than dose-proportional manner with increasing dose (see Clinical Pharmacology Review, by Suryanarayana Sista et al, dated 08/27/2014, page 28).

4.2 Adverse event profile through all Phases 1 of development

The following is a review of those abuse-related TEAEs reported in Phase 1 Study Reports 20110168, 20120133, 20120136, 20120135, 20080397, 20110121, and 20120341. These 7 Phase 1 studies assessed doses of evolocumab in healthy volunteers only, therefore limiting any potential effects due to commitment use of other drugs, which is typical among a treatment population assessed during Phase 2 and Phase 3 of drug development. Phase 1 studies not included in this assessment were Studies 20110234 and 20120101 because both of these studies only assessed placebo formulations; as such evolocumab was not administered. Also not included was Study 20080398 because the study did not

evaluated evolocumab in healthy volunteers (e.g., subjects with hypercholesterolemia on stable doses of statins).

Evolocumab was administered subcutaneously to subjects by using a vial and syringe, multiple AI/pens (up to 3), an automated mini-doser (AMD), or a PFS. As previously specified, this submission is for the approval of the AI/pens and PFS. PK/PD, safety and clinical information was included for the vial and syringe and the AMD. However, the vial and syringe is not intended for commercialization, (b) (4)

For those abuse-related TEAEs reported in Phase 1 Study Reports 20110168, 20120133, 20120136, 20120135, 20080397, 20110121, and 20120341, among the system organ categories that are mentioned dizziness AEs are recorded in three of the seven safety studies:

- 1) Study 20110168: evolocumab at 140 mg (total 420) via 3 AI/Pen, N=145, dizziness counts of N=1 (0.7%) and 420 mg via 1xAMD, N=144, dizziness counts N = 2 (1.4%), no placebo
- 2) Study 20120133: evolocumab at 140 mg via 1xAI/Pen, N=91, dizziness counts of N=1 (1.1%) and PFS/prefilled syringe (N=91), dizziness N = 3 (3.3%), no placebo
- 3) Study 20120136: evolocumab at 140 mg given at 2 treatment periods (Period 1 and 2) at different times at 56 days apart, via 2xAI/Pen Period 1, N=20, dizziness counts of N=1 (5.0%) and 1xPFS Period 2 (N=18), dizziness counts of N = 0 (0%), no placebo

Based on the AE data submitted by the Sponsor, no other abuse related AE was reported among the three studies; therefore, dizziness was not accompanied with any other abuse-related AE. In addition, total count of dizziness for each study was reported at less than 5% of the sample population. The Sponsor's AE reports for the other 4 Phase 1 studies (i.e., 20120135, 20080397, 20110121, and 20120341) revealed no abuse related AEs, and over the 7 Phase 1 studies assessed (including those not included in the current assessment), there were no adverse events reported as serious, and there weren't any subjects that discontinued a study due to an adverse event. Furthermore, there were no incidences of unaccounted medication, deaths and overdoses.

The AE profile of evolocumab support that it has no abuse potential.

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/s/

JOVITA F RANDALL-THOMPSON
07/15/2015

MICHAEL KLEIN
07/15/2015



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: June 4, 2015

From: Christos Mastroyannis, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Acting Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Acting Division Director,
Division of Pediatric and Maternal Health

To: The Division of Metabolism and Endocrinology Products (DMEP)

Drug: REPATHA (evolocumab)

BLA: 125522

Subject: Maternal Health Labeling Recommendations

Applicant Amgen, Inc

Materials Reviewed:

August 27, 2014, BLA– Original BLA submission from Amgen

April 23, 2015, Annotated Draft Labeling Text to comply with PLLR requirements by
Amgen

May 15, 2015, Pharmacology/Toxicology review for BLA 125522

May 15, 2015, Annotated Labeling by PT reviewer

Consult Question: “DMEP requests assistance to apply the new Pregnancy and Lactation Labeling Rule requirements to the REPATHA labeling. This is a new BLA seeking approval for the treatment of dyslipidemia and HoFH (Homozygous Familial

Hypercholesterolemia). Two PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitors for hypercholesterolemia applications are currently under review by the Division. The Division will consider this labelling (PLLR inclusion) as the model for the other PCSK9 applications.”

INTRODUCTION

On August 27, 2014, Amgen submitted BLA 125522 for REPATHA (evolocumab) subcutaneous injection, to be used for the treatment of adult patients with hyperlipidemia or mixed dyslipidemia and in pediatric patients 12 years of age and older with homozygous familial hypercholesterolemia (HoFH).

DMEP consulted Division of Pediatric and Maternal Health (DPMH) to review the proposed Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in the REPATHA product labeling.

On December 4, 2014, the Food and Drug Administration (FDA) published the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling”, also known as the Pregnancy and Lactation Labeling Rule (PLLR)¹. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all drug products that are subject to the 2006 Physician Labeling Rule (PLR)², to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR will take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to the PLLR format.

This review provides recommended revisions and structuring of information related to the Pregnancy (8.1), Lactation (8.2), and Females and Males of Reproductive Potential (8.3) subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with PLLR regulatory requirements.

BACKGROUND

Product Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secretory serine protease that homeostatically regulates the amount of plasma LDL-C by interacting with the LDL receptor. After binding to and internalization, PCSK9 directs the LDL receptor to lysosomal degradation, inhibiting its recycling to the hepatocyte surface and thus catabolism of plasma

¹ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

² Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

LDL-C³. REPATHA is a human monoclonal IgG2. It belongs to the group of PCSK9 inhibitor antibodies. REPATHA binds selectively and with high affinity to PCSK9 and inhibits circulating PCSK9 from binding to the low density lipoprotein (LDL) receptor (LDLR), on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. Increasing liver LDLR levels result in associated reductions in serum LDL-C

REPATHA has an approximate molecular weight (MW) of 144 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells. It is a sterile, preservative-free, clear to opalescent, colorless to yellowish solution. Each 1 mL Single-Use PFS and Single-Use Prefilled SureClick® Autoinjector for injection (for subcutaneous use) contains 140 mg evolocumab, 220 mM proline, 20 mM acetate, 0.01% polysorbate 80, Water for Injection and sodium hydroxide to a pH of 5.0.

Cholesterol and Pregnancy

Cholesterol is important for embryo-fetal development. The fetus derives the substantial proportion (at least 80%) of its cholesterol needs from endogenous synthesis rather than via the maternal circulation⁴. Across multiple species including humans, the rates of cholesterol synthesis in the fetus are much greater than in the adult⁵.

Whether mediated by dietary intervention or by genetic mutations resulting in 50% reduction in maternal serum LDL-C, no negative effects on embryo-fetal development have been observed in children born to mothers with low cholesterol throughout pregnancy⁶. High synthetic rate in the fetus and/or the placenta provides sufficient cholesterol to maintain sterol-independence from maternal sources⁷. These findings are consistent with the results from the evolocumab monkey study in which maternal serum LDL-C was lowered ~70% throughout pregnancy, but there were no effects on embryo-fetal (or postnatal) development. This finding may indicate a low risk for embryo-fetal harm in humans.

Monoclonal antibodies do not effectively cross the human placenta during organogenesis (early pregnancy/first trimester), but do cross the placenta in significant amounts in second and third trimester (ICH M3 [R2], 2009⁸). In addition, various barriers to embryo-fetal

³ Santos RD and Watts GF. Familial hypercholesterolemia: PCSK9 inhibitors are coming. *The Lancet*, 2015;385(9965):331-340

⁴ Bartels A and O'Donoghue K. Cholesterol in pregnancy: a review of knowns and unknowns. *Obstetric Med.* 2011; 4:147-151.

⁵ Dietschy JM, Turley SD, and Spady DK. Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans.1993; *J Lipid Res.* 34:1637-1659.

⁶ Hormanics GE, Smith TJ, Zhang SH, et al. Targeted modification of the apolipoprotein B gene results in hypobetalipoproteinemia and developmental abnormalities in mice. *Proc. Natl. Acad. Sci. USA.* 1992; 90:2389-2393.

⁷ Woollett LA. Maternal cholesterol in fetal development: transport of cholesterol from the maternal to the fetal circulation. *Am J Clin Nutr.* 2005;82:1155-1161.

⁸ International Conference on Harmonization, Topic M3(R2), Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals, June 2009.

exposure indicate also that following administration to a male subject, monoclonal antibodies would be non-bioavailable to the developing fetus.

Risk of exposure to the fetus from male-mediated drug transfer

Human-risk assessments on male-mediated drug transfer (paternal exposure; for paternal exposure pregnancies, time of exposure is the trimester of partner's pregnancy in which the male subject was on study drug) are based upon assumptions derived from extrapolation from small molecule drugs and/or endogenous moieties (e.g., naturally occurring IgG). The risk of drug exposure via semen to achieve meaningful pharmacological levels in a pregnant woman or in the conceptus is negligible^{9,10}.

HUMAN REPRODUCTION AND PREGNANCY DATA

Discussion: Review of Data

A search of published literature was performed and no information was found reporting the use of REPATHA in pregnant women.

The applicant has conducted no studies of REPATHA in pregnant women. In addition, no studies have been conducted to determine whether evolocumab is present in breast milk or to assess the effects of evolocumab in breast-fed infants.

From the current submission, two subjects, one in Study 20101154 and one in Study 20110271 (HoFH) who became pregnant were discontinued from the studies. As per the clinical reviewer, Eileen Craig, M.D., across the evolocumab clinical program, 7 pregnancies following maternal evolocumab exposure and 9 following paternal evolocumab exposure have been reported out of approximately 6,800 subjects enrolled in evolocumab clinical studies. Outcomes of the maternal exposure pregnancies include full-term birth without complications (1 pregnancy), unknown (3 ongoing pregnancies-1 lost to follow up, 1 unknown and 1 follow up ongoing), spontaneous abortion not otherwise specified (1 pregnancy), ectopic pregnancy (1 pregnancy), elective termination for personal reasons (1 pregnancy). See Table 1 below for a listing of pregnancy outcomes. There have been no reports of use during lactation in the clinical program. The applicant in the 120 days safety report has reported three additional pregnancies (all paternal exposure). SID 15466036008/ Study 20110110, SID 15566093004/ Study 20110110 and SID 11542003004/ Study 20120138, all with paternal exposure; there were no pregnancy related adverse events reported at the time. All 3 male partners who took REPATHA continued with the study and the investigational drug.

As this is the first marketing application for evolocumab, there is no postmarketing data at this time.

⁹ Klemmt L, Scialli AR. The transport of chemical in semen. Birth Defects Res B Dev Reprod Toxicol. 2005; 74:119-131.

¹⁰ Banholzer ML, Buergin H, Wandel C, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partners. J Transl Med. 2012; 10:129.

Table 1: Tabular Summary of Pregnancies Following Evolocumab Exposure in the Clinical Program through 01 April 2014

Subject Number	Study Number	Time of Evolocumab Exposure ^a	Birth Outcome (normal delivery, abortion, unknown, etc.)
Maternal Exposure Pregnancies			
11411001012	20110114	1st Trimester	Full-term birth without complications
15516066007	20110110	1st Trimester	Spontaneous abortion not otherwise specified
15516066007	20110110	1st Trimester	Ectopic pregnancy
15516066007	20110110	8 months prior to conception	Elective termination for personal reasons
15466036003	20101154	1st Trimester	Lost to follow-up
15466043005	20110110	1st Trimester	Unknown (ongoing)
23356001010	20110271	1 st Trimester	Follow up (ongoing)
Paternal Exposure Pregnancies			
10913001001	20110109	1st Trimester	Full-term birth without complications
15416016005	20110110	Unknown	Lost to follow-up
10916302038	20120138	1st and 2nd Trimesters	Lost to follow-up
10916302038	20110109	1st Trimester	Spontaneous abortion
15466013002	20101154	1st Trimester	Lost to follow-up
15866003018	20110110	1st, 2nd, and 3rd Trimesters	Full-term birth without complications
16866009037	20110168	1st Trimester	Elective termination not otherwise specified
15466030002	20110110	1st and 2nd Trimesters	Spontaneous abortion not otherwise specified
15856001009	20110110	1st, 2nd, and 3rd Trimesters	Full-term birth without complications

BLA 125522 Original Submission, August 27, 2014. Summary of clinical safety, Table 104, p:324

Reviewer’s comment

These limited clinical data are insufficient to draw meaningful safety conclusions about the effects of REPATHA (evolocumab) during pregnancy and lactation.

A. REPATHA and Pregnancy

Animal Data

As per Pharmacology –Toxicology reviewer, Calvin (Lee) Elmore, PhD, in the review entered in DARRTS on May 15, 2015, the toxicology program was appropriately designed to evaluate the clinical risks associated with chronic administration of evolocumab. Fertility and early embryonic assessments were conducted in hamsters. Fertility assessments were also included in the 6-month monkey toxicity study. Evaluation of evolocumab administration during the periods of embryofetal and pre/postnatal development was conducted in monkeys. In developmental toxicology studies in monkeys, when pregnant females were exposed to evolocumab, measurable evolocumab concentrations in serum were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating that evolocumab, like other IgG antibodies, crosses the placental barrier. Published literature with monoclonal

antibodies in humans indicate that they are unlikely to cross the placenta in the first trimester; however, they are likely to cross the placenta in increasing amounts in the second and third trimester.

Evolocumab was tested in pregnant monkeys during the period of embryofetal development to parturition with subcutaneous administration once every two weeks at doses that provide exposure multiples of 30-, 12- and 5.2-fold the recommended human doses of 140 mg once every 2 weeks(Q2W), 420 mg once weekly (QW) and 420 mg once every 2 weeks (Q2W). Offspring were followed to 6 months of infancy. No evaluation of the infant immune system was conducted. No clear drug-related toxicity was observed in mother or infant monkeys.

Reviewer's comment

From the animal data during the drug development process as per P/T review, evolocumab, like other IgG antibodies, crosses the placenta and circulates in the fetal blood at comparable levels to maternal serum. REPATHA does not appear to be associated with adverse reactions in either the mother or the fetus. However, in animal studies with other PCSK9 inhibitor antibody class drugs in development, humoral immune suppression was observed in infant monkeys exposed to the drug in utero, as per P/T reviewer. Further evaluation of REPATHA administration during pregnancy should be conducted. DPMH recommends a pregnancy pharmacovigilance program when REPATHA is used during pregnancy to evaluate pregnancy outcomes and infant adverse reactions at least up to one year of life because of the potential significant number of pregnant women who may be exposed to the drug.

B. REPATHA and Lactation

The Drugs and Lactation Database (LactMed)¹¹ was searched for available lactation data on with the use of REPATHA. No entries were found. There is no evidence up to now if REPATHA is present in human milk. Human IgG is present in human milk, but published data suggests that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Reviewer Comment:

It is not known whether REPATHA (evolocumab) is present in human milk. Because many drugs and immunoglobulins are present in human milk and because of the potential for adverse effects from REPATHA in nursing infants, a decision should be made whether to discontinue nursing or discontinue REPATHA, taking into account the potential benefit of REPATHA to the mother or

¹¹ United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

the potential benefit of breast-feeding to the infant. Further studies may provide a better understanding of use of REPATHA during lactation.

C. REPATHA and Females and Males of Reproductive Potential

Infertility

There are no human data available regarding the effects of REPATHA on fertility. No fertility or early embryonic development studies were conducted. Evolocumab is not expected to interact directly with DNA. Effects of evolocumab on fertility and mating were assessed in hamsters. No effects of evolocumab (subcutaneous dosing once every two weeks) on mating, fertility, estrous cycling, or male reproduction were observed at exposure multiples up to 30-, 12- and 5.3-fold the plasma exposures measured in humans at the 140 mg Q2W, 420 mg QW and 420 mg Q2W evolocumab doses. Effects on fertility were also assessed in the 6-month chronic monkey toxicity study at exposure multiples of up to 744-, 300- and 134-fold compared to the recommended human doses of 140 mg Q2W, 420 mg QW and 420 mg Q2W, respectively. No effects on fertility endpoints were observed. (b) (4)

Contraception

There are no recommendations for contraception use with REPATHA in labeling because no drug-associated risks to the pregnant women or the fetus have been demonstrated.

CONCLUSION/RECOMMENDATIONS

1. Review of the literature revealed no data with REPATHA use in pregnant or lactating women. Because of the potential significant number of pregnant women who may be exposed to REPATHA, DPMH recommends further evaluation of REPATHA use during pregnancy. DPMH recommends a pregnancy pharmacovigilance program when REPATHA is used during pregnancy to evaluate pregnancy outcomes and infant adverse reactions at least up to one year of life.
2. The Pregnancy (8.1) and Lactation (8.2) subsections of labeling were structured to be consistent with the PLLR. (b) (4)

Additional edits are provided below.

DPMH refers to the BLA action for final labeling.

DPMH has the following recommendations for REPATHA labeling:

5 Warnings and Precautions, Section 5.1

Reviewer's comment:

DPMH does not recommend inclusion of such statements because there are no relevant safety risks that rise to the level of warnings and precautions.

8.1 Pregnancy

Risk Summary

There are no available data on use of Repatha in pregnant women to inform a drug-associated risk. In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were subcutaneously administered evolocumab from organogenesis through parturition at dose exposures up to ^{(b) (4)} times the exposure at the maximum recommended human dose of 420 mg every ^{(b) (4)}. Measurable evolocumab serum concentrations were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating that evolocumab, like other IgG antibodies, crosses the placental barrier.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In cynomolgus monkeys, no effects on embryo-fetal or postnatal development (up to 6 months of age) were observed when evolocumab was dosed during organogenesis to parturition at 50 mg/kg once every two weeks by the subcutaneous route at exposures 30-, 12- ^{(b) (4)}-fold the recommended human doses of 140 mg every two weeks, 420 mg once ^{(b) (4)} respectively, based on plasma AUC. No test of humoral immunity in infant monkeys was conducted with evolocumab.

8.2 Lactation

Risk Summary

There is no information regarding the presence of evolocumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggests that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Repatha and any potential adverse effects on the breastfed infant from Repatha or from the underlying maternal condition.

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

/s/

CHRISTOS MASTROYANNIS
06/30/2015

TAMARA N JOHNSON
06/30/2015

LYNNE P YAO
07/02/2015



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 30, 2015

From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGRID, ODE, CDRH

To: Kati Johnson
Division of Metabolism and Endocrine Products, Office of New Drugs, CDER

Via: Keith Marin and Ryan McGowan
Combination Products Team Leaders, GHDB, DAGRID, CDRH

Rick Chapman
Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH

Subject: BLA 125522 Repatha (Evolomumab) /Applicant: Amgen
CDRH Tracking: ICC1400577-Supplement 4, Supplement 5 and Supplement 6

Indication: 1. Treatment of Primary Hyperlipidemia and Mixed Dyslipidemia
2. Treatment of Homozygous Familial Hypercholesterolemia (HoFH)

Background: This memo is an addendum to CDRH/ODE/GHDB consult memo dated 9/14/2014.

On February 23, 2015, GHDB was contacted by CDER/DMEPA regarding human factors errors noted during the simulated use trials where the users have noted the autoinjector is harder to trigger. There were 81 successful attempts out of 97 total attempts for the 1st time users and the error is that patients are not exerting enough pressure against the skin in order to trigger the shot. This was especially voiced by those users who are more experienced using other autoinjectors, so they are not expecting the amount of pressure required for this product. [REDACTED] (b) (4)

The question is did the 2nd time users have the same problems exerting enough pressure?

Of the errors, 16 occurred during the first visit, and 4 occurred during the second visit:

	Trained			Untrained		
Number of errors in Visit 1	Patients	HCPs	Caregivers	Patients	HCPs	Caregivers
	1	3	1	3	5	3
Number of errors in Visit 2	Patients	HCPs	Caregivers	Patients	HCPs	Caregivers
	0	2	2	N/A	N/A	N/A

As a result of the above inquiry, CDRH/ODE/GHDB formulated 5 deficiency questions which were sent to Amgen on 3/2/2015 as an IR request:

From: Johnson, Kati

Sent: Monday, March 02, 2015 3:20 PM

To: Kubasak, Marc (mkubasak@amgen.com)

Cc: Johnson, Kati

Subject: BLA 125522, Repathy (evolocumab) Device/human factor IR

Hi Marc,

During the review of the BLA Human Factors Studies, it appears that participants had a hard time pressing and holding the autoinjector at the injection site long enough to deliver the full dose of Repatha. We noted that even after training, some caregivers and clinicians still had the same trouble on the 2nd visit.

Please address the following questions:

1. During the clinical trial, were there any adverse events, technical issues, or malfunctions associated with the injector or syringe presentations? If yes, what was the root cause analysis and assessment?
2. During the clinical trials with the users were using the autoinjectors in non-clinical setting, did they demonstrate the same pattern or problem (not exerting enough pressure and hold time)? If yes, did it continue toward later part of the clinical trial w/o decrease? What was the average injection time during the clinical trials? Have the prefilled autoinjectors used in the clinical trials and during the human factors study been aged in real-time or undergone accelerated aging before use?
3. Please provide summary tables of the PFS and autoinjector design requirements delineating clear traceability between requirements and verification activities.
4. Please provide risk analysis and management/mitigation information for all device constituent parts of the combination product before and after clinical trial/HF testing to include any changes instituted as a result of these tests and its subsequent validation. Note that risk analysis information as composed by third party suppliers will not be sufficient unless such documentation contains risks which have been analyzed in the context of the delivery of the specific medication to be delivered through the device constituent part.

5. Please provide shelf-life and durability testing information to demonstrating that the combination product (prefilled autoinjector and pre-filled syringe products) will perform as specified after shipping and aging (real-time and/or accelerated aging studies) to the desired expiration point. Specifically, we are interested in the functionality of the device constituents in meeting the design specifications after these extreme conditions (for example: right before shelf-life expiration of the combination product).

As usual, please provide a timeline when you can.

Thanks, Kati

Kati Johnson

Senior Regulatory Project Manager

From: Johnson, Kati

Sent: Wednesday, April 01, 2015 6:17 AM

To: Kubasak, Marc (mkubasak@amgen.com)

Cc: Johnson, Kati

Subject: BLA 125522, Repatha (evolocumab) request for clarification re: 3/25/2015 response it FDA IR

Hi Marc,

Below is from the CDRH reviewer:

I am looking over the 158 page IR response from Amgen. I need some clarification from Amgen:

It was noted that the AI/Pen had only 5 device failures (glass syringe breaking after autoinjector injection) out of (b) (4) injections but there were (b) (4) device complaints for the AI/Pen. What percentage of these complaints were "autoinjector activation" and what exactly is defined as "autoinjector activation"? Does "autoinjector activation" mean that patients persistently had problems triggering the AI? We note that the (b) (4) device complaints due to AI/Pen is an increase of (b) (4) complaints during the 120 day safety update after the original clinical trial. Is there a further breakdown regarding what percentage of these complaints were due to 1st injection and which are due to subsequent injection? (b) (4)

Also needing clarification, (b) (4) please describe what are the extremes mentioned here that resulted in the glass syringe breakage? Was the glass shattering contained in the AI or did it cause harm/injury to the user/bystander?

As always, please provide a timeline for when you can respond.

Thanks, Kati

Kati Johnson

Senior Regulatory Project Manager

Amgen responded to our 3/2/2015 IR request on 3/25/2015 (ICC 1400577-S4):

1. Most of device related adverse events were injection site reactions and this event rate was considered low, with no apparent differences in incidences between subjects receiving evolocumab compared with those subjects receiving placebo, regardless of the device used.

The data show a very low incidence of failures identified with the AI/Pen and none with the PFS. The 5 AI/Pen failures were all associated with 1 cause code (“syringe broken during/after use”). The root cause of these failures was identified as (b) (4)

Table 1. Cumulative (as of Initial BLA 01 April 2014) Complaint Issues and Failures Received for the Evolocumab Clinical Program (AI/Pen; PFS)

Device	Number of Device Injections	Number of Complaint Issues	Number of Failures
PFS	(b) (4)		0
AI/Pen	(b) (4)		3

Note: This table includes aggregated data from clinical studies 20110110, 20110114, 20110115, 20110116, 20110117, 20120138, 20120348 and 20120356. (Data cutoff 01APR14)

Table 2. Cumulative (as of 120-day Safety Update 01 July 2014) Complaint Issues and Failures Received for the Evolocumab Clinical Program (AI/Pen; PFS)

Device	Number of Device Injections	Number of Complaint Issues	Number of Failures	Failure Rate
PFS	(b) (4)		0	0%
AI/Pen	(b) (4)		5	0.006%

Device Injection Data Modified from 120-Day Safety Update Tables 14-5.5.404, 14-5.5.406, 14-5.5.407, 14-5.5.408, and Table 14-5.2.1 of Study 20110271 and ISS tables 14-5.5.401, 14-5.5.402, 14-5.5.403, (Data cut off 01JUL 2014)

CDRH/ODE/GHDB Assessment of Q1 Response: Request for further information regarding the broken syringes.

From: Johnson, Kati [<mailto:Kati.Johnson@fda.hhs.gov>]

Sent: Wednesday, April 01, 2015 3:17 AM

To: Kubasak, Marc

Cc: Johnson, Kati

Subject: BLA 125522, Repatha (evolocumab) request for clarification re: 3/25/2015 response it FDA IR

Hi Marc,

Below is from the CDRH reviewer:

I am looking over the 158 page IR response from Amgen. I need some clarification from Amgen:

It was noted that the AI/Pen had only 5 device failures (glass syringe breaking after autoinjector injection) out of (b) (4) injections but there were (b) (4) device complaints for the AI/Pen. What percentage of these complaints were "autoinjector activation" and what exactly is defined as "autoinjector activation"? Does "autoinjector activation" mean that patients persistently had problems triggering the AI? We note that the (b) (4) device complaints due to AI/Pen is an increase of (b) (4) complaints during the 120 day safety update after the original clinical trial. Is there a further breakdown regarding what percentage of these complaints were due to 1st injection and which are due to subsequent injection? (b) (4)

Also needing clarification, (b) (4) please describe what are the extremes mentioned here that resulted in the glass syringe breakage? Was the glass shattering contained in the AI or did it cause harm/injury to the user/bystander?

As always, please provide a timeline for when you can respond.

Thanks, Kati

Kati Johnson

Senior Regulatory Project Manager

2. Tracking of each subject's injection time was not included in the clinical studies, as the feasibility and reliability of clinicians and subjects tracking such a measurement would be difficult. However, data from the large clinical study program, which included AI/Pen drug administration in the clinic and home-use settings, showed that subjects, caregivers, and clinicians were effectively administering drug via the AI/Pen and subjects were receiving an effective dose, as evidenced by the pharmacodynamic data collected. Specifically, evidence included analysis of resulting low-density lipoprotein cholesterol (LDL-C) levels and assessments of the users' ability to administer a full dose of evolocumab in a home-use setting. The collected clinical data demonstrated safety and efficacy of evolocumab using prefilled AI/Pens aged in real-time before use, confirming usability and functional durability, during the clinical study program.

The pushing and triggering failures observed in the HFE/UE study occurred in a clinical setting, where an actual injection and investigational product delivery occur, than in the

HFE/UE study setting, which is a simulated injection. In the HFE/UE study, participants do not have the feedback of an actual needle penetration and the feeling of investigational product subcutaneous administration to signal that the injection was successfully initiated and completed. In addition, the methodology in the HFE/UE study sought to approximate the worst case scenario, which is that users would receive minimal or even no training.

Two phase 3 clinical studies assessed the effective administration of evolocumab by subjects or caregivers in the home-use setting. The results for the AI/Pen demonstrated that, after training, subjects were able to successfully self-administer a full dose of evolocumab (140 mg or 420 mg) in a home-use setting using 1 AI/Pen to administer the 140 mg dose or 3 separate 1.0 mL injections administered within 30 minutes to deliver the 420 mg dose. This was demonstrated both from results of querying of subjects on their ability to successfully administer a full dose and by measuring the resulting LDL-C reductions. In the AI/Pen group in Study 20120348, the percentage (95% CI) of subjects who fully administered evolocumab in a home-use setting according to subject report was 95.9% (88.7%, 98.6%) at week 2 and 91.9% (83.4%, 96.2%) at week 4. In Study 20120356, the percentage (95% CI) was 93.9% (86.5%, 97.4%) at week 4 and 92.7% (84.9%, 96.6%) at week 8; one subject (1.2% [0.2%, 6.6%]) administered a full dose outside the planned visit window. Note that full administration of a dose could have not occurred for various reasons, not just issues with administration. Subjects who discontinued investigational product prior to their scheduled administration were also recorded as not receiving a full dose; subject discontinuation accounted for more than half of the subjects who did not receive a full dose.

For each of the clinical studies, both the duration from subassembly component manufacture to assembly of the prefilled AI/Pen, as well as the duration from AI/Pen assembly to final dosing date, are provided. (b) (4)

(b) (4) Stability data are currently available to support an initial proposed commercial expiry of (b) (4) months for the subassemblies at (b) (4) °C and an additional 24 months for the assembled prefilled AI/Pen at 5°C. The clinical data collected used devices that had undergone real-time aging ranging from (b) (4) days for the subassembly shelf-life and (b) (4) days for the prefilled AI/Pen. For the long-term safety and efficacy studies (20110110 and 20120138), the average duration from subassembly storage to prefilled AI/Pen assembly ranged from (b) (4) days and the average duration from AI/Pen assembly to final dosing ranged from (b) (4) days.

Clinical Study Number	Study Descriptor	Duration of Subassembly Storage Prior to AI/Pen Assembly		Longest Duration from AI/Pen Assembly to Dosing (days)	
		Average (days)	Range (days)	Average (days)	Range (days)
20120133	Healthy subject PK AI/Pen to PFS				
20120341	Intrinsic factors				
20110110	Long-term efficacy and safety (OLE)				
20110233	HoFH				
20110271	Severe familial hypercholesterolaemia				
20110114	Monotherapy				
20110115	Combination therapy				
20110116	Statin intolerant				
20110117	HeFH				
20120138	Long-term efficacy and safety (OLE)				
20120348	PFS vs. AI/Pen				
20120356	AMD vs. AI/Pen				
N/A	Human Factors Summative Study for AI/Pen 1.0				
N/A	Human Factors Summative Study for AI/Pen 1.5				

(b) (4)

AI/Pen = autoinjector/pen; AMD = automated mini-doser; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; PFS = prefilled syringe; OLE = open-label extension; PK = pharmacokinetic
N/A = Not applicable. All units had the same duration.

CDRH/ODE/GHDB Assessment of Q2 Response: Adequate, no further issues.

- The tables in Appendix A through Appendix C provide traceability between the device design requirements and device design verification and validation activities for the:
 - Evolocumab Prefilled Syringe (Table 25)
 - Evolocumab AI/Pen 1.0 (Table 26)
 - Evolocumab AI/Pen 1.5 (Table 27)

All verification and validation activities listed have passing or acceptable results to pre-established acceptance criteria with risk based disposition of non-passing results.

CDRH/ODE/GHDB Assessment of Q3 Response: We reviewed Tables 25-27, no further issues.

- Amgen has reassessed risks and updated risk management deliverables as identified in section Device Risk Management Summary Introduction. In those reassessments Amgen has taken into account data from HFE/UE studies and clinical trials. Table 8 for AI/Pen 1.0, Table 9 for AI/Pen 1.5, and Table 10 for PFS document specific hazards that have been changed or added in successive revisions of the user risk assessment documents as the direct results of such data. The latest versions of the Use Risk Assessment Summary Reports were provided in the BLA: Device Design Validation [AI/Pen 1.0], Device Design Validation [AI/Pen 1.5], and Device Design Validation [PFS].

In one case (Table 8, Item 1), Amgen undertook a design change of the AI/Pen as a direct result of user experience. The observation that the AI/Pen 1.0 [REDACTED] (b) (4) [REDACTED] led directly to the development of AI/Pen 1.5, specifically to mitigate this hazard. The AI/Pen 1.5 subsequently underwent extensive testing in both verification and validation activities to ensure that this failure mode was successfully mitigated as summarized in Device Design Development [AI/Pen 1.5], Device Design Verification [AI/Pen 1.5] and Device Design Validation [AI/Pen 1.5]. Risk levels associated with these presentations continue to be acceptable based on established Amgen criteria.

CDRH/ODE/GHDB Assessment of Q4 Response: We reviewed the information provided and have no further issues.

5. The functionality of the device constituents in meeting the design specifications after exposure to shipping and aging through the intended shelf-life for the prefilled AI/Pen and PFS is supported by accelerated aging (ASTM F1980) studies (prefilled AI/Pen only), real-time stability studies, and transport validation including evaluation both immediately after simulated transport and after long-term storage at the recommended storage condition.

The following information is presented for the AI/Pen:

1. Results are provided from accelerated aging conducted per ASTM F1980, Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices. Data are presented for AI/Pen 1.0 and AI/Pen 1.5. These data confirmed that only injection time from the design specifications may be stability indicating for system functionality.
2. Stability results can be accessed from the updated 3.2.P.8.3 Overview [140 mg/mL AI/Pen]. Data are presented through 24 months for the AI/Pen 1.0 filled with PFS primary stability lots and 12 months data for the AI/Pen 1.0 and AI/Pen 1.5 filled with PFS validation stability lots. Both injection time and deliverable volume were assessed for functionality. Data confirmed that there were no changes in deliverable volume and no trend in injection time over the duration of the studies supporting the proposed 24 month shelf-life.

The 24 month shelf life at 5°C for the AI/Pen 1.0 and AI/Pen 1.5 has been established through evaluation of real time stability testing of the AI/Pen 1.5 and AI/Pen 1.0. The two devices are functionally identical and the design differences are identified in 3.2.R.2.2, Device Design Development [AI/Pen 1.5] [REDACTED] (b) (4) [REDACTED]

[REDACTED] It is expected that any effect of aging would be the same for both designs and therefore stability results for AI/Pen 1.0 can be applied to support the 24 month shelf life at 5°C for the AI/Pen 1.5.

3. Results are provided from design verification testing for AI/Pen 1.0 and AI/Pen 1.5 performed per ASTM D4169 shipping tests and in accordance with ISO 11608-1 for shock and vibration. Data for injection time, deliverable volume, needle extension, and visual examination confirmed no change in functionality after simulated transportation.

4. Results are provided in 3.2.P.8.3 Transport Study – Primary Lot [140 mg/mL AI/Pen] from the real-time stability storage study at 5°C through 24 months for AI/Pen 1.0 placed on stability after simulated transport. Both injection time and deliverable volume were assessed for functionality. Data confirmed that there was no change in deliverable volume and no trend in injection time over the duration of the studies supporting the proposed 24 month shelf-life.

The following information is presented for the PFS:

1. Results can be accessed in 3.2.P.8.3 Overview [140 mg/mL PFS]. Data are presented through 24 months data for the PFS primary stability lots manufactured at the clinical/commercial manufacturing site (ATO) and 12 months data for the PFS validation stability lots manufactured at both proposed commercial sites (AML (b) (4) and ATO). Data confirmed that there were no changes in breakloose or extrusion forces over the duration of the studies, and the device passed the sterility and container closure integrity tests, supporting the proposed 24 month shelf-life.
2. Results are provided from design verification testing after transportation simulation per ASTM 4169. Data for breakloose and extrusion forces and visual examination confirmed no change in functionality after simulated transportation. Results are provided from container closure integrity (CCI) testing before and after manufacturing assembly of plunger rod, packaging, and transport simulation per ASTM 4169. Data for vacuum decay testing after transportation confirmed no change in functionality after simulated transportation.
3. Results are provided in 3.2.P.8.3 Transport Study – Primary Lot [140 mg/mL PFS] from the real-time stability storage at 5°C through 24 months for 140 mg/mL PFS placed on stability after simulated transport. Breakloose and extrusion forces, sterility and container closure integrity were assessed. Data confirmed that there was no trend in breakloose and extrusion forces and that sterility and container closure integrity testing passed over the duration of the studies supporting the proposed 24 month shelf-life.

Summary of Shipping and Aging Studies to Support Shelf-life - AI/Pen Accelerated Aging (ASTM F1980)

(b) (4)

Accelerated aging studies included testing units after storage at an elevated temperature of (b) (4) °C which was used to rapidly stress the device components to confirm functionality at simulated end of shelf-life.

At each time point (b) (4) subassemblies were evaluated. At all time points the subassemblies were visually inspected and equilibrated for one hour at ambient conditions prior to being assembled with a syringe filled with either evolocumab or saline that had been stored at 5°C.

Extrapolation of Durations From Accelerated Storage at (b) (4) °C to Recommended Storage at 5°C

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

The stability testing demonstrates the proper functioning at each test time point after storage at the recommended storage condition of 5°C ((b) (4) units are tested per time point). Based on the results of accelerated aging testing, it has determined that injection time is stability-indicating for system functionality. Deliverable volume is also tested to confirm complete delivery of the intended dose through shelf life. All other attributes tested during accelerated aging demonstrate that the mechanical characteristics of the subassemblies are static and not relevant to real time stability testing. Therefore, injection time and deliverable volume stability testing verifies the long term effect of the device function.

**Table 14. Stability Data for 140 mg/mL AI/Pen 1.0 Drug Product [ATO]
Primary Lot Stored at 5°C**

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)			
			0	6	12	24
0010146417	Injection Time		(b) (4)			
	Deliverable Volume					

* Triplicate testing from release results used as stability T=0 time point

**Table 15. Stability Data for 140 mg/mL AI/Pen 1.0 Drug Product [AML] (b) (4)
Validation Lots Stored at 5°C**

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)		
			0	6	12
0010193952	Injection Time		(b) (4)		
	Deliverable Volume				
0010193953	Injection Time		(b) (4)		
	Deliverable Volume				
0010193954	Injection Time		(b) (4)		
	Deliverable Volume				

**Table 16. Stability Data for 140 mg/mL AI/Pen 1.5 Drug Product [AML (b)(4)]
Validation Lots Stored at 5°C**

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)		
			0	6	12
0010193955	Injection Time	(b)(4)			
	Deliverable Volume				
0010193956	Injection Time				
	Deliverable Volume				
0010193957	Injection Time				
	Deliverable Volume				

**Table 17. Stability Data for 140 mg/mL AI/Pen 1.5 Drug Product [ATO]
Validation Lots Stored at 5°C**

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)		
			0	6	12
0010190116	Injection Time	(b)(4)			
	Deliverable Volume				
0010190115	Injection Time				
	Deliverable Volume				
0010190118	Injection Time				
	Deliverable Volume				

Table 18. Shipping/Distribution Testing (ASTM D4169), ISO 11608-1 Drop/Vibration Testing & 23°C Temperature Testing – AI/Pen

Test	Specification	No Stress Testing		After Stress Testing													
		ISO 11608-1 23 ± 5°C Temp Testing		Shipping/Distribution Testing (ASTM D4169)		ISO 11608-1 Drop Testing		ISO 11608-1 Vibration Testing									
		AI/Pen 1.0	AI/Pen 1.5	AI/Pen 1.0	AI/Pen 1.5	AI/Pen 1.0	AI/Pen 1.5	AI/Pen 1.0	AI/Pen 1.5								
Deliverable Volume (mL)	(b)(4) Average Maximum Minimum StDev	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)	(b)(4)								
Injection Time (Seconds)	Average Maximum Minimum StDev																
Needle Extension (mm)	Average Maximum Minimum StDev																
Visual	Pass/Fail									Pass							

Results from storage at 5°C through 24 months for AI/Pen 1.0 placed on stability after simulated transport demonstrate that both injection time and deliverable volume do not change over the duration of the studies supporting the proposed 24 month shelf-life.

**Table 19. Stability Data for 140 mg/mL AI/Pen 1.0 Drug Product [ATO]
Primary Lot Post Transport Study Stored at 5°C**

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)				
			0 (pre-transport)	0.3	6	12	24
0010146417	Injection Time	(b)(4)					
	Deliverable Volume						

CDRH/ODE/GHDB Assessment of Q5 Response—autoinjector: Test results for T4 (T4, equivalent to (b)(4)) have a single injection time failure of (b)(4) seconds, which is well past requested shelf-life label claim of 24 months.

There is an effect on injection time for both AI/Pen 1.0 and AI/Pen 1.5. The trend shows (b)(4) of injection time over the simulated aging period. However, the observed (b)(4) doesn't result in an out of specification condition within the 24 month storage criteria.

All test results passed the acceptance criteria at all time points through T3, equivalent to (b)(4). The T3 test results support storage of the subassemblies a (b)(4)°C for (b)(4) years followed by storage of the assembled device with drug product for 2 years at 5°C. These results met the shelf life requirements for AI/Pen 1.0 and AI/Pen 1.5.

The combined data package supports that the functionality of the AI/Pen after exposure to extreme conditions (shipment and storage through proposed expiry).

Results are provided from the real time stability storage at 5°C, including 24 months for the primary PFS lots and 12 months for the PFS validation lots at both commercial sites (AML (b)(4) and ATO). All BLE results in the tables below meet the design specification of (b)(4)N. The results also demonstrate that container-closure integrity is maintained over the duration of the stability studies, thus supporting the 24 month shelf life.

**Table 20. Stability Data for 140 mg/mL PFS Drug Product [ATO]
Primary Lots Stored at 5°C**

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)			
			0	6	12	24
0010135345	Breakloose (N)	(b)(4)				
	Extrusion (N)					
	Sterility					
	CCI by Dye Ingress					
0010138260	Breakloose (N)					
	Extrusion (N)					
	Sterility					
	CCI by Dye Ingress					
0010138262	Breakloose (N)					
	Extrusion (N)					
	Sterility					
	CCI by Dye Ingress					

Table 21. Stability Data for 140 mg/mL PFS Drug Product [AML] (b) (4)
Validation Lots Stored at 5°C

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)		
			0	6	12
0010193587	Breakloose (N)	(b) (4)			
	Extrusion (N)				
	Sterility				
	CCI by Dye Ingress				
0010193589	Breakloose (N)				
	Extrusion (N)				
	Sterility				
	CCI by Dye Ingress				
0010193590	Breakloose (N)				
	Extrusion (N)				
	Sterility				
	CCI by Dye Ingress				

Table 22. Stability Data for 140 mg/mL PFS Drug Product [ATO]
Validation Lot Stored at 5°C

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)		
			0	6	12
0010188062	Breakloose (N)	(b) (4)			
	Extrusion (N)				
	Sterility				
	CCI by Dye Ingress				

Breakloose and Extrusion Force Testing After Transport

To verify that the commercial representative packaging protects the evolocumab PFS, 75 fully assembled PFS, with CMC placebo, were packed into the commercial packaging: sealed blister tray in a sealed carton with 2 folded leaflets. The placebo is viscosity matched to AMG 145 drug product, making it sufficient for BLE measurement for indication device constituent damage. These 75 units were then packed (b) (4) and shipped from ATO to a third party test vendor.

The units were individually opened and visually inspected for damage to cartons, blisters and PFS. The PFS were visually inspected for broken or cracked syringes and intact needle shields. No units failed visual inspection. Sixty of these units were then tested, at room temperature, against the (b) (4) N breakloose and peak extrusion force design specification (Table 23).

Table 23. Breakloose and Extrusion Force After ASTM D4169 Transportation Simulation – PFS; Acceptance Criteria (b) (4) N

Test	Transport Simulation BLE Tested @ 25C; N = 60		
	Mean	Max	Std. Dev.
Breakloose (N)	(b) (4)		
Extrusion (N)	(b) (4)		

**Table 24. Stability Data for 140 mg/mL PFS Drug Product [ATO]
Primary Lot Post Transport Study Stored at 5°C**

Lot	Test Method	Stability Acceptance Criteria	Time Point (months)				
			0 (pre-transport)	2.5	6	12	24
0010138280	Breakloose (N)						(b) (4)
	Extrusion (N)						(b) (4)
	Sterility						(b) (4)
	CCI by Dye Ingress						(b) (4)

CDRH/ODE/GHDB Assessment of Q5 Response—Prefilled Syringe: No change in breakloose and extrusion forces, sterility and container closure integrity after exposure to transportation and long term storage at 5°C supporting the proposed shelf-life of 24 months for the PFS. Functionality of the prefilled syringe maintained. No further issues.

Amgen responded on 4/27/2015 to the Agency's IR questions from 4/1/2015 (ICC 1400577-S5):

FDA question: It was noted that the AI/Pen had only 5 device failures (glass syringe breaking after autoinjector injection) out of (b) (4) injections but there were (b) (4) device complaints for the AI/Pen. What percentage of these complaints were "autoinjector activation" and what exactly is defined as "autoinjector activation"? Does "autoinjector activation" mean that patients persistently had problems triggering the AI? We note that the (b) (4) device complaints due to AI/Pen is an increase of (b) (4) complaints during the 120 day safety update after the original clinical trial. Is there a further breakdown regarding what percentage of these complaints were due to 1st injection and which are due to subsequent injection? (b) (4)

Activation Issues Breakdown by Injection and Schedule

The complaints database did not capture subject dosing schedule (1st or subsequent dose); however, of the (b) (4) complaint records, (b) (4) contained dosing schedule data. (b) (4) of the complaints stated that it was the subject's first dose and (b) (4) stated that it was a subsequent dose. The relatively low number of complaints on the first dose may be contributed to the health care provider administering a subject's first dose, in cases where that happened. As this data was not proactively collected for complaints, Amgen can't make definitive statements from this data. Amgen stated they will start to collect this data on all complaints and report findings post approval in the annual report.

Of the (b) (4) complaints reported, (b) (4) complaints had available data for dosing schedule (Q2W or QM). Of the (b) (4) complaints, (b) (4) of the subjects were on Q2W and (b) (4) were on QM dosing schedules. For subjects on Q2W injections, only a single AI/Pen is used per dose and subjects on QM injections use 3 AI/Pen per dose. There is a higher opportunity for complaints to occur on the QM dosing schedule due to the increased number of AI/Pen injections per dose.

Table 1. AI/Pen Activation Cause Codes and Number of Complaints

Amgen Cause Code	Reported Complaint	Number of Complaints
(b) (4)		

Table 2. Comparison of BLA (01 April 2014) to 120-day Safety Update (01 July 2014) Complaints Received for the Evolocumab Clinical Program (AI/Pen)

Date of Data Cut Off	Device	Number of Attempted Device Injections	Number of Complaints	Complaint Rate
01APR2014	AI/Pen	(b) (4)		
01APR2014 to 01JUL2014	AI/Pen	(b) (4)		
Total	AI/Pen	(b) (4)		

Note: For the 01APR2014 data cut off, this table includes aggregated data from clinical studies 20110109, 20110110, 20110114, 20110115, 20110116, 20110117, 20120138, 20110168, 20110233, 20120348 and 20120356. For the 01JUL2014 data cut off, this table includes aggregated data from clinical studies 20110109, 20110110, 20110114, 20110115, 20110116, 20110117, 20120138, 20110168, 20110233, 20120348, 20120356 and 20110271.

Device Injection Data Modified from 120-Day Safety Update Tables 14-5.5.404, 14-5.5.406, 14-5.5.407, 14-5.5.408, and Table 14-5.2.1 of Study 20110271 and ISS Tables 14-5.5.401, 14-5.5.402, 14-5.5.403, (Data cut off 01JUL 2014)

Complaint Issue and Failures Source: Product Complaints Metrics and Trending (Data snap shot 01JUL14)

CDRH/ODE/GHDB Assessment: There is a decrease in the complaint rate from April to July of 2014 which may indicate that subjects did not persistently have problems triggering the AI/Pen suggesting that use errors related to activation will reduce as users get more experience with the device.

FDA Question: Also needing clarification, (b) (4)

(b) (4) please describe what are the extremes mentioned here that resulted in the glass syringe breakage? Was the glass shattering contained in the AI or did it cause harm/injury to the user/bystander?

Figure 1. Syringe Breakage Failure Modes



Forensics analysis of the broken syringes indicates the failures originated at [redacted] (b) (4)

[redacted]

[redacted] (b) (4)

In other evolocumab clinical trials through 30 March 2015, there are (b) (4) additional AI/Pen failures for syringe breakage out of approximately (b) (4) AI/Pen injection attempts. This brings the occurrence rate from approximately 0.006%. Of the additional (b) (4) failures, there were (b) (4) reported ADEs. These (b) (4) ADEs occurred in 6 subjects, were non-serious, and resolved. All were CTCAE Grade 1 events (mild) except 1 that was Grade 2. (b) (4)

[redacted]

Verbatim Adverse Event Term	Number of ADEs	Serious or Non-Serious	Device Related or Non-Device Related	CTCAE Severity Grade	Adverse Event Outcome
Painful Injection	1	Non-Serious	Device Related	Grade 1	Resolved
Bleeding at Injection Site	1	Non-Serious	Device Related	Grade 1	Resolved
Puncture Site Bleeding	1	Non-Serious	Device Related	Grade 1	Resolved
AI Needle retained in skin	1	Non-Serious	Device Related	Grade 1	Resolved
Injection Device Malfunction	1	Non-Serious	Device Related	Grade 1	Resolved
Needle from Autoinjector Broke and was Partiel in Upper Leg	1	Non-Serious	Device Related	Grade 1	Resolved
Device Malfunction (Needle Broke Off)	1	Non-Serious	Device Related	Grade 2	Resolved

Common Terminology Criteria for Adverse Events (CTCAE)

CDRH/ODE/GHDB Assessment: Amgen described the rare occurrence of glass syringe breaking and its suspected mechanism with the associated adverse events (syringe/AI needles breaking off/detaching due to the syringe breakage and embedding itself in the patients' injection sites). This could possibly occur when (b) (4)

. We should get more information from Amgen:

-Does Amgen know if the syringe breakage events happened (b) (4)

(b) (4)

Email sent to Kati Johnson on 5/1/2015 stating the above request.

IR Response received from Amgen regarding the glass syringe breakage issue on 5/14/2015 (ICC 1400577-S6):

Amgen's Response to Question 1

In review of the (b) (4) syringe breakage events (also referred to as syringe breakage complaints and syringe breakage complaint issues) noted in the response to questions submitted on 27 April 2015 (Sequence No. 0044), (b) (4) of these reported complaints had information provided on (b) (4) Where this information was reported, all devices (b) (4) were reported by the user to have been warmed for 30 minutes (per the IFU) prior to the reported syringe breakage event.

Root cause analysis determined that the breakage is a result of

(b) (4)

CDRH/ODE/GHDB Assessment: Glass breakage from physical impact force is happening in rare incidents and it would be hard to further improve the design of the device when it is occurring at less than 0.01% of the time. Although the occurrence rate of these glass syringe breakage is very low (<0.01%), there is the reported incidence of staked needle detaching after breakage and embedding/retaining in the patient's injection site.

Defer to CDER review team regarding whether there should be a warning statement in the label regarding glass syringe may occur resulting in needle detachment and possible temporary retention of the needle in the injection site.

Lana Shiu, M.D.



Digitally signed by Lana
L. Shiu -S
Date: 2015.05.18
12:31:03 -04'00'

Branch Chief



Richard C. Chapman -S
c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300
369827, cn=Richard C. Chapman
-S
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
07/01/2015
OND PM entering CDRH rview into DARRTS



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: June 25, 2015

Reviewer: Jibril Abdus-Samad, PharmD, Labeling Reviewer
Office of Biotechnology Products Jibril Abdus-samad -S

Through: Sang Bong Lee, PhD, Quality Reviewer
Division of Biotechnology Review and Research IV

Application: BLA 125522/0 **Sang Bong Lee -S**

Product: Repatha™ (evolocumab)
Repatha™ SureClick® (evolocumab)

Applicant: Amgen Inc.

Submission Dates: August 27; November 24, 2014; May 5, 22, and June 24, 2015

Digitally signed by Jibril Abdus samad S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus samad S
Date: 2015.06.25 15:40:42 -0400

Digitally signed by Sang Bong Lee-S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=Sang Bong Lee-S, ou=0.9.2342.19200300.100.1.1=2000339306, cn=Sang Bong Lee-S
Date: 2015.06.26 16:17:43 -04'00'

Executive Summary:

The container labels and carton labeling for Repatha (evolocumab) and Repatha SureClick (evolocumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia, USP 38/NF 33 [May 1, 2015 to July 31, 2015]. Labeling deficiencies were identified, mitigated, and resolved. The container labels and carton labeling submitted on June 24, 2015 are acceptable.

Background and Summary Description:

The Applicant, Amgen Inc. (Amgen), submitted BLA 125552 Repatha (evolocumab) on August 27, 2014. Table 1 lists the proposed product characteristics of Repatha (evolocumab).

Table 1: Proposed product characteristics of Repatha (evolocumab)

Trade Name	Repatha
Proper Name	evolocumab
Indication	<ul style="list-style-type: none">- Reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with primary hyperlipidemia or mixed dyslipidemia- Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia
Dose	<ul style="list-style-type: none">- Primary or mixed dyslipidemia: Administer 140 mg every 2 weeks or 420 mg once monthly in the upper arm, thigh, or the abdomen.- Homozygous familial hypercholesterolemia: Administer 420 mg either once monthly or every 2 weeks.
Route of Administration	Subcutaneous injection (upper arm, thigh, or the abdomen)
Dosage Form	Injection
Strength and Container-closure	140 mg/mL single-use prefilled syringes (PFS) 140 mg/mL single-use autoinjector
Storage and Handling	Store in a refrigerator at 36° to 46° F (2°C to 8°C) in original carton. If removed from the refrigerator, Repatha™ should be kept at controlled room temperature (up to 25°C (77°F)) in the original carton and must be used within 30 days. Do not freeze. Do not expose to extreme heat.

Materials Reviewed:

- PFS Container Label
- PFS Blister Tray Labeling
- Autoinjector Container Label
- PFS Carton Labeling
- Autoinjector Carton Labeling

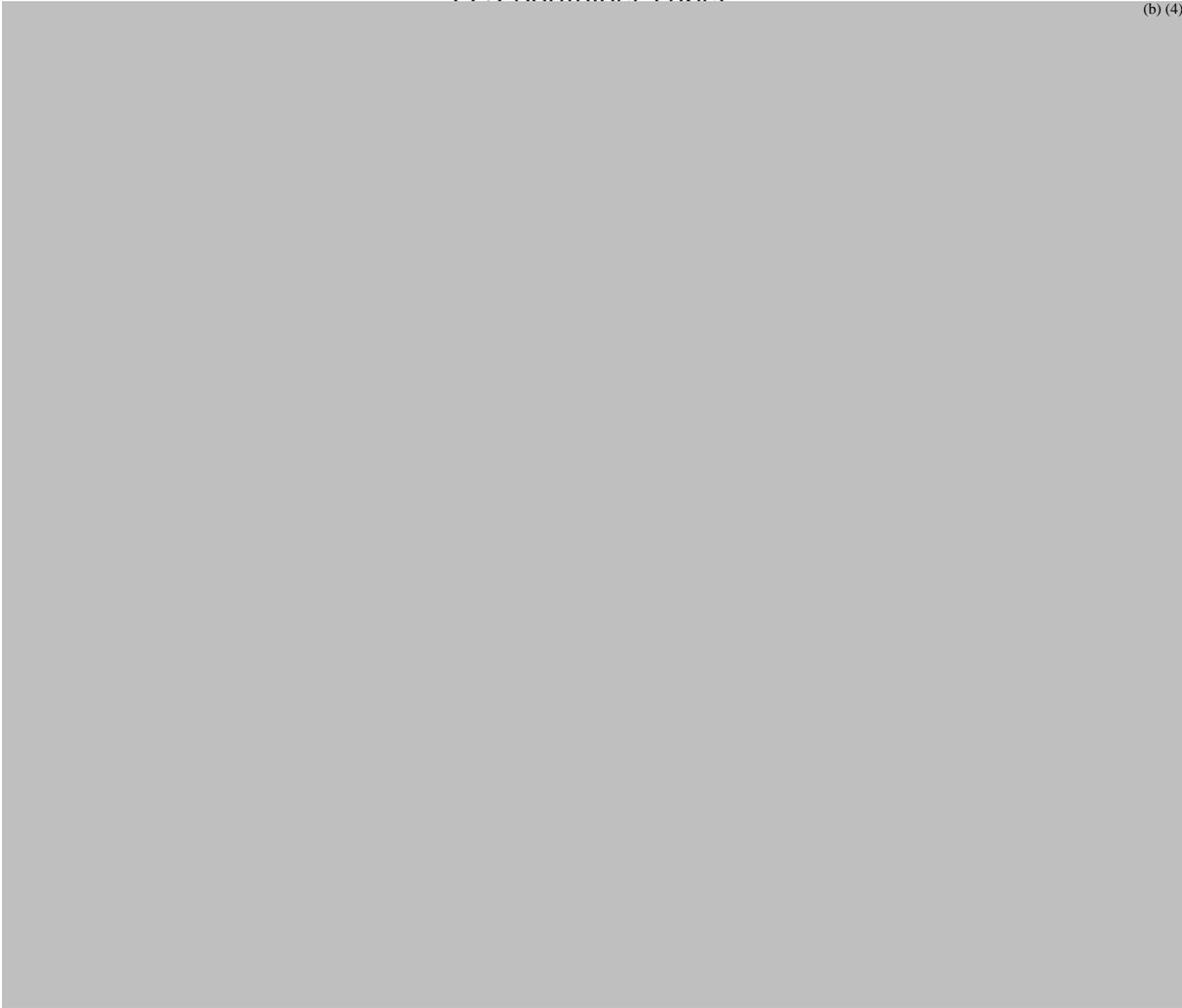
*Note the Applicant submitted container labels and carton labeling on November 24, 2014, as well as revised versions on May 5 and 22, 2015.

Start of Sponsor Material

Proposed labels and labeling submitted November 24, 2014

PFS Container Label

(b) (4)



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

PFS Container Label

Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum:

1. name (expressed either as the proper or common name); *conforms.*
2. lot number or other lot identification; *conforms.*
3. name of the manufacturer; *conforms.*
4. for multiple dose containers, the recommended individual dose; *not applicable.*
5. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms.*

PFS Blister Tray Labeling and Autoinjector Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

- (1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *conforms.*
- (2) The name, address, and license number of manufacturer; *conforms.*
- (3) The lot number or other lot identification; *conforms.*
- (4) The expiration date; *conforms.*
- (5) The recommended individual dose, for multiple dose containers; *not applicable.*
- (6) The statement: "Rx only" for prescription biologicals; *conforms.*

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable for blister tray label. See Partial Label section above for PFS container label.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *conforms.*

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms.*

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms.*

D. 21 CFR 201.6 Drugs; misleading statements; *conforms.*

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence]. **does not conform.**

OBP Requests:

The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). *Applicant revised as requested.*

F. 21 CFR 201.15 Drugs; prominence of required label statements; **does not conform.**

OBP Requests:

Increase the prominence of the strength that currently appears below the proper name per 21 CFR 201.15(a)(6) by increasing the font size. *Applicant revised as requested.*

Increase the prominence (font size) of the route of administration statement "For Subcutaneous Use Only" to clearly identify how the drug product should be safely used and handled. *Applicant revised as requested.*

Add the dosage form, Injection, to appear under the proper name, evolocumab, in the identical font size and color as the proper name. Due to lack of space on the small prefilled syringe (PFS) container label, omission of the finished dosage form is acceptable.

Applicant Response: Amgen accepts the proposed revision to add the dosage form "Injection" in the identical font size and color as the proper name. Amgen has proposed to include (b) (4)

OBP Response: Relocate the dosage form, Injection, to appear under the proper name, evolocumab. To further clarify, the proper name for CDER- regulated biological products should not include the finished dosage form. The finished dosage form, Injection, can appear on the line below the proper name. Consider the following options to create space:

- Slightly decrease the font size of the dosage form "Injection"
- Relocate the manufacturer information to the right-side of the labeling.
- Relocate "Rx Only" to the upper portion of the label near the NDC.

Applicant revised as requested.

Unbold the Rx only statement as it competes in prominence with other important information on the labels and labeling. *Applicant revised as requested.*

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*

H. 21 CFR 201.25 Bar code; *conforms.*

I. 21 CFR 201.50 Statement of identity; *conforms.*

J. 21 CFR 201.51 Declaration of net quantity of contents; **does not conform.**

OBP Requests:

Revise the strength statement in the blue circle from (b) (4) to read 140 mg/mL as per USP 12/1/2014 – 4/30/2015 General Chapters: <1> Injections. The strength per total volume should be the primary and prominent expression on the principal display panel for single-dose injectable products. *Applicant revised as requested.*

(b) (4) Consider adding this to the net quantity statement at the top of the blister tray labeling. For example: 1 x 1 mL Prefilled Syringe. *Applicant revised as requested.*

K. 21 CFR 201.55 Statement of dosage; *conforms.*

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*

(b) (4) However OBP recommends removing (b) (4) from PFS blister tray labeling to improve readability of other important information on the label.

OBP Request: Delete [REDACTED] (b) (4) from blister tray labeling to improve readability of other important information on the label. [REDACTED] (b) (4) *Applicant* revised as requested.

Start of Sponsor Material

(b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

II. Carton

A. 21 CFR 610.61 Package Label:

- a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *conforms*.
- b) The name, addresses, and license number of manufacturer; *conforms*.
- c) The lot number or other lot identification; *conforms*.
- d) The expiration date; *conforms*.
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.
- f) The number of containers, if more than one; *conforms*.
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; **does not conform**.

OBP Request: Revise the strength statement in the blue circle from (b)(4) to "140 mg/mL", as per USP General Chapters: <1> Injections. The strength per total volume should be the primary and prominent expression on the principal display panel for single-dose injectable products. *Applicant revised as requested.*

- h) The recommended storage temperature; **does not conform**.

OBP Request: Include complete storage instructions if Repatha is removed from the refrigerator, as mentioned in Section 16 of the Prescribing Information labeling. The complete instructions should provide instructions separate instructions for patients to store at room temperature. Additionally, provide a space for documentation of the date of initial removal from the refrigerator. For example:

Pharmacy

Store refrigerated 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.

Patient/Caregiver

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. If needed, Repatha™ may be kept at room temperature (up to 25°C (77°F)) in the original carton and must be used within 30 days. Use space below to record the date removed from the refrigerator.

Applicant revised as requested.

To decrease crowding of the PDP, relocate the patient/caregiver storage information to the rear or side panel, similar to the presentation on the PFS carton labeling. *Applicant revised as requested.*

- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms.*
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *conforms.*
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms.*
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable.*
- m) The type and calculated amount of antibiotics added during manufacture; *not applicable.*
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable.*
- o) The adjuvant, if present; *not applicable.*
- p) The source of the product when a factor in safe administration; *not applicable.*

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Not applicable*.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Repatha is a monoclonal antibody for in vivo use.*

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor: The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. *Not applicable*.

E. 21 CFR 610.67 Bar code label requirements: Biological products must comply with the bar code requirements at §201.25 of this chapter; *conforms*.

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] **does not conform**.

OBP Request: The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). *Applicant revised as requested.*

J. 21 CFR 201.15 Drugs; prominence of required label statements; **does not conform**.

OBP Requests:

Relocate the route of administration, For Subcutaneous Use Only, to appear under the the statement, 140 mg/mL Prefilled Syringe. *Applicant revised as requested.*

Increase the prominence (font size) of the route of administration statement "For Subcutaneous Use Only". *Applicant revised as requested.*

Add the dosage form, Injection, to appear under the proper name, evolocumab, in the identical font size and color as the proper name. Due to lack of space on the small prefilled syringe (PFS) container label, omission of the finished dosage form is acceptable.

Applicant Response: Amgen accepts the proposed revision to add the dosage form "Injection" in the identical font size and color as the proper name. Amgen has proposed to include ^{(b) (4)}

[Redacted]

OBP Response: Relocate the dosage form, Injection, to appear under the proper name, evolocumab. To further clarify, the proper name for CDER- regulated biological products should not include the finished dosage form. The finished dosage form, Injection, can appear on the line below the proper name. Consider the following options to create space:

- Slightly decrease the font size of the dosage form “Injection”.
- Relocate “Rx Only” to the upper portion of the label near the NDC.
- Relocate “Keep out of the sight and reach of children” to the right-side of the principal display panel (PDP).

Applicant revised as requested.

Unbold the Rx only statement as it competes in prominence with other important information on the labels and labeling. *Applicant revised as requested.*

K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

L. 21 CFR 201.25 Bar code label requirements; *conforms*.

M. 21 CFR 201.50 Statement of identity; *conforms*.

N. 21 CFR 201.51 Declaration of net quantity of contents; **does not conform**.

OBP Requests:

Revise the strength statement in the blue circle from (b) (4) to read 140 mg/mL as per USP 12/1/2014 – 4/30/2015 General Chapters: <1> Injections. The strength per total volume should be the primary and prominent expression on the principal display panel for single-dose injectable products. *Applicant revised as requested.*

(b) (4) Consider adding this to the net quantity statement at the top of the label. For example: 1 x 1 mL Prefilled Syringe. *Applicant revised as requested.*

O. 21 CFR 201.55 Statement of dosage; *conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; **does not conform**.

OBP Request: Revise the list the names of the inactive ingredients in alphabetical order in the following format “inactive ingredient (amount)” per USP, General Chapters: <1091> Labeling of Inactive Ingredients. For example:

Each single-dose prefilled syringe contains a 1 mL deliverable volume of 140 mg evolocumab in a sterile, preservative-free solution, containing acetate (1.2 mg), polysorbate 80 (0.1 mg), proline (25 mg), in Water for Injection, USP. Sodium hydroxide may be used to adjust to pH 5.0.

Note use of the term “single-dose” and deletion of the hyphen (1-mL to 1 mL) and trailing zero (0.10 mg to 0.1 mg). Additionally, delete “(s)” from “Water for Injection(s), USP” so that it appears as “Water for Injection, USP”.

Applicant revised as requested.

CDER Labeling Recommendations

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences. The Applicant revised as requested unless noted otherwise.

A. General Comments for labels and labeling

1. OBP finds [REDACTED] (b) (4) within “Repatha” can lead to the “R” being misinterpreted as a [REDACTED] (b) (4). OBP concurs with DMEPA’s recommendation to remove the [REDACTED] (b) (4).
[REDACTED]
[REDACTED] 1
2. Images should represent the actual dosage form (i.e., prefilled syringe or prefilled autoinjector) and reflect the true size and color; schematic or computer-generated images should not be used. We recommend removing the images of the prefilled syringe and prefilled autoinjector on the carton labeling (and carton tray labeling for the prefilled syringe).² If an actual image of the prefilled syringe or prefilled

¹ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. [REDACTED] (b) (4)

² Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>. “If an image is used on the PDP, the image should appear at the bottom of the label and should not compete in size or prominence with the proprietary and/or nonproprietary name and strength information. Images should...reflect the true size, color, and imprint.”

autoinjector is used, the image should not compete in size or prominence with the proprietary name and/or established name and strength.

3. Change any reference from "single-use" to "Single-Dose" to ensure that the entire dose is delivered and the injectable device is not reused. "Single-Dose" is the appropriate term per USP, General Chapters: <659> PACKAGING AND STORAGE REQUIREMENTS.

Applicant Response: Amgen believes the term "Single-Dose" could provide confusion since there are potentially two doses that a patient could be prescribed, 140 mg and 420 mg. The 140 mg dose is a single injection from either a PFS or an AI, but the 420 mg dose requires 3 injections from a PFS or an AI. For the 420 mg dose, Amgen thinks that it is misleading to a patient to indicate that a single PFS or AI is a "single dose" when it actually would be a partial dose.

For these reasons, Amgen proposes to retain the term "Single-Use" rather than changing to "Single-Dose". The term "Single-Use" is in accordance with standards that are recognized by FDA and seems more accurate. In addition, Amgen believes the term "Single-Use" provides sufficient direction to help ensure that the entire dose is delivered and the injectable device is not reused.

OBP Response: We find your proposal to maintain "Single-Use" is *acceptable*.

Moving forward, note that FDA is planning to publish a Draft Guidance for *Appropriate Package Type Terms for Injection Drugs or Biological Products in Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers*
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417290.pdf>

B. Carton Labeling for Autoinjector

1. Delete (b) (4) that appears below the proper name.
2. Add "SureClick" to appear with "Repatha". For example:

Repatha SureClick
(evolocumab)
Injection
140 mg/mL
Prefilled Autoinjector

For Subcutaneous Use Only.
Single-Use Only.

C. PFS Blister Tray Labeling

1. Relocate the statements, "Sterile Solution – No Preservative", to the right side of the panel.
2. Add the statement "Single-Use Only" to the PDP" below the route of administration statement. "For Subcutaneous Only".
3. Delete (b) (4) above the barcode and replace with the text that appears on the carton labeling.

D. Autoinjector Container Label

1. (b) (4) above the barcode and replace with the text that appears on the carton labeling.
2. Delete "(b) (4)" that appears below the proper name.
3. Add "SureClick" to appear with "Repatha". For example:

Repatha SureClick
(evolocumab)
140 mg/mL
Prefilled Autoinjector
For Subcutaneous Use Only.
Single- Use Only.

4. Revise the font color of all the text under the strength statement. The font appears as a (b) (4) color which has a poor contrast with the background and is difficult to read. The (b) (4) font color on the previous version (submitted November 27, 2014) was easy to read.

Applicant's Response: The submitted draft label represents the mockup of the actual label. This is a clear label that is meant to be placed on a blue autoinjector. The draft label provided with this submission has a side-by-side view of the actual label and what the actual label will look like once placed on the blue autoinjector (1.14.1.1 – Autoinjector – 140 mg Autoinjector Barrel Label). The white text contrasts with the blue background addressing the concerns of the agency. *Acceptable.*

E. PFS Container Label

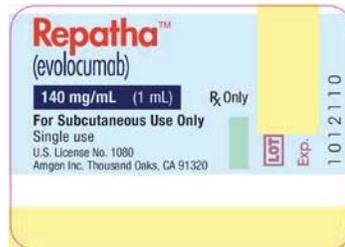
1. We consider the PFS Container Label a partial label due to its small size per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability
2. Add the route of administration statement "For Subcutaneous Use Only" to appear below the strength statement.
3. Delete the (b) (4) and replace with Single-Use Only.

Conclusions

The container labels and carton labeling for Repatha (evolocumab) and Repatha SureClick (evolocumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia, USP 38/NF 33 [May 1, 2015 to July 31, 2015]. Labeling deficiencies were identified, mitigated, and resolved. The container labels and carton labeling submitted on June 24, 2015 are acceptable (see below).

PFS Container Label

<\\cdsesub1\evsprod\bla125522\0066\m1\us\prefilled-syringe-140mg-syringe-label.pdf>



PFS Blister Tray Labeling

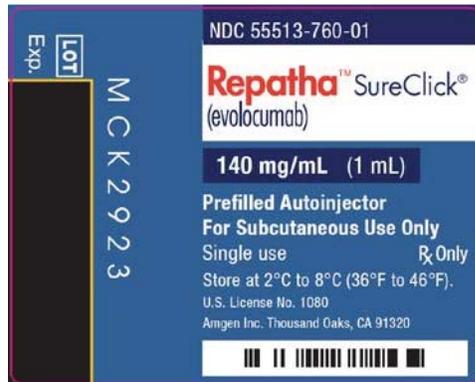
<\\cdsesub1\evsprod\bla125522\0066\m1\us\prefilled-syringe-140mg-blister-tray-topweb.pdf>



Autoinjector Container Label
<\\cdsesub1\evsprod\bla125522\0066\m1\us\autoinjector-140mg-barrel-label.pdf>



*Note: The submitted draft label represents the mockup of the actual label. This is a clear label that is meant to be placed on a blue autoinjector. The draft label provided with this submission has a side-by-side view of the actual label and what the actual label will look like once placed on the blue autoinjector. The white text contrasts with the blue background addressing the concerns of the agency (see below).



PFS Carton Labeling
 \\cdsesub1\evsprod\bla125522\0066\m1\us\prefilled-syringe-140mg-
 dispensing-carton.pdf



PFS Carton Labeling (replacement pack)
 \\cdsesub1\evsprod\bla125522\0066\m1\us\prefilled-syringe-140mg-
 dispensing-carton-replace-dose.pdf



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: June 25, 2015

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: BLA 125522

Product Name and Strength: Repatha (evolocumab) Injection, 140 mg/mL [Prefilled Syringe]
Repatha SureClick (evolocumab) Injection, 140 mg/mL [Autoinjector]

Submission Date: June 24, 2015

Applicant/Sponsor Name: Amgen

OSE RCM #: 2014-1869-1

DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH

DMEPA Team Leader: Yelena Maslov, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container label and carton labeling (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.¹

2 CONCLUSIONS

The revised container label and carton labeling is acceptable from a medication error perspective.

¹ Mistry M. Label and Labeling Review for Repatha and Repatha SureClick (BLA 125522). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Apr 13. 56 p. OSE RCM No.: 2014-1869.

7 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/

MISHALE P MISTRY
06/25/2015

YELENA L MASLOV
06/25/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 4, 2015

TO: Eileen Craig, M.D., Clinical Reviewer
James P. Smith, M.D., Deputy Director (Acting)
Kati Johnson, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125522

APPLICANT: Amgen

DRUG: Evolocumab/ AMG 145 (fully human monoclonal immunoglobulin G2 [IgG2] directed against human proprotein convertase subtilisin/kexin type 9 [PCSK9])

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of primary hyperlipidemia and mixed dyslipidemia, and for the treatment of homozygous familial hypercholesterolemia (HoFH).

CONSULTATION REQUEST DATE: October 3, 2014

CLINICAL INSPECTION SUMMARY GOAL DATE: June 26, 2015*

DIVISION ACTION GOAL DATE: August 27, 2015*

PDUFA DATE: August 27, 2015*

*There is another PCSK9 application under review and it has been requested to move up the consult review due date to June 1, 2015 for decision goal date of July 24, 2015.

I. BACKGROUND

Amgen, Inc. is seeking approval of evolocumab (formerly referred to as AMG 145), a fully human IgG2 monoclonal antibody directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9), for the treatment of primary hyperlipidemia and mixed dyslipidemia. Amgen is also seeking approval for the treatment of homozygous familial hypercholesterolemia (HoFH).

Amgen requested an institutional review board (IRB) Waiver for foreign sites not meeting all the requirements contained in 21 CFR Part 56. On July 24, 2012, FDA granted the waiver and applied the waiver to all current and subsequent foreign clinical studies conducted under IND 105188.

Inspections were requested for the following three clinical studies:

- **20110109** A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Long-term Tolerability and Durable Efficacy of AMG 145 on LDL-C in Hyperlipidemic Subjects

This study was conducted at 88 study centers in the US, Canada, Australia, South Africa, and Europe. A total of 2120 subjects were screened, 905 subjects were randomized and 855 subjects completed the study. The first subject enrolled on January 5, 2012, and the last subject completed the study on November 7, 2013. The primary endpoint was percent change from baseline in low-density lipoprotein cholesterol (LDL-C) at Week 52.

- **20110114** A Double-blind, Randomized, Placebo- and Ezetimibe-controlled, Multicenter Study to Evaluate Safety and Efficacy of Lipid Lowering Monotherapy With AMG 145 in Subjects With a 10-Year Framingham Risk Score of 10% or Less

This study was conducted at 71 centers in the US, Denmark, Belgium, Australia, Canada, France, South Korea, Taiwan, and Turkey. A total of 1059 subjects were screened, 615 subjects were randomized and 598 subjects completed the study. The first subject was enrolled on January 21, 2013 and the last subject completed follow-up on October 29, 2013. The co-primary endpoints were percent change from baseline in LDL-C at Week 12 and mean percent

change from baseline in LDL-C at Weeks 10 and 12.

- **20110115** A Double-blind, Randomized, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia

This study was conducted at 198 centers in the US, Czech Republic, United Kingdom, Canada, Denmark, Germany, Russia, Hungary, Italy, Australia, Netherlands, Belgium, Sweden, Switzerland, Spain, France, and Hong Kong. A total of 3591 subjects were screened, 2067 subjects were first randomized, 1899 were re-randomized and 1826 completed the study. The first subject was enrolled on January 15, 2013 and the last subject completed follow-up on December 4, 2013. The co-primary endpoints were percent change from baseline in LDL-C at Week 12 and mean percent change from baseline in LDL-C at Weeks 10 and 12.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of BLA 125522 in accordance with Compliance Programs 7348.810 and 7348.811. General instructions were also provided with the assignments.

II. RESULTS (by Site):

Name of CI/ Site #	Protocol # and # of Subjects Randomized	Inspection Date	Preliminary Classification
Vivek Awasty Site 1-65YIRL (66080)	20110115 29 subjects	10/27 – 11/05/2014	Voluntary Action Indicated (VAI)
Site 1-59VDW6 (66002)	20110115 13 subjects	11/17 – 11/20/2014	Voluntary Action Indicated (VAI)
Michael Bolognese Site 1-51Q (66402)	20110109 35 subjects 20110114 24 subjects	11/04 – 11/06/2014	No Action Indicated (NAI)
Tomas Hala Site 1-1AF9XT (23201)	20110109 42 subjects 20110115 25 subjects	01/05 – 01/09/2015	No Action Indicated (NAI)
Annesofie Krogsaa Site 1-4HRP5T (25202)	20110115 50 subjects 20110114 56 subjects	1/12 – 1/20/2015	No Action Indicated (NAI)

	20110109 33 subjects		
Ben Lasko Site 1-55N7TT (16300)	20110109 41 subjects 20110114* 14 subjects <i>Not indicated on consult but added to inspection</i>	1/05/– 1/16/2015	No Action Indicated (NAI)
Amgen	20110109 20110114 20110115	11/12 – 11/14/2014	No Action Indicated (NAI)

Key to Classifications

NAI = No deviation from regulations

VAI = Deviation(s) from regulations

OAI = Significant deviations from regulations; data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending letter to site.

1. Vivek R. Awasty, M.D.

Awasty Research Network
980 South Prospect Street
Suite 2
Marion, OH 43302-6225

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. All subject records were reviewed.
- b. General observations/commentary:** Dr. Awasty is listed as being Principal Investigator for two separate sites for Study 20110115. The sites are about 3 hours away from each other. His original site was Site 1-65YIRL (66080). Site 1-59VDW6 (66002) was under Awasty Research Network LLC partnered with Harrison Research Center with a sub-Investigator at Harrison Community Hospital in Cadiz, Ohio (records are in Cadiz and there is a separate clinical research staff). Dr. Robert G. Looby was listed as the original clinical investigator for Site 1-59VDW6 (66002) (1572 signed on October 10, 2012) and was present during most of the study. Dr. Awasty was initially listed as a

sub-Investigator; however, he did not directly participate in the conduct of the trial at Site 1-59VDW6 (66002) until Dr. Looby's departure. The site was then transitioned to Dr. Awasty when Dr. Looby left the site. Dr. Awasty signed the 1572 for this site on October 4, 2013. The FDA field investigator inspected both sites under Dr. Awasty as separate entities.

For **Site 1-65YIRL (66080)**, there were 46 subjects screened, 30 subjects enrolled (1 lost to follow-up), 29 dosed and 29 subjects that completed the study. The IRB of record was [REDACTED] (b) (4). All approvals were in order. The first subject signed the informed consent on June 4, 2013.

All subjects enrolled appeared to have met inclusion/exclusion criteria. The subject records contained adequate information about each subject's exposure to the test article, as well as observations and data of their condition throughout their participation in the study. Overall, individual subject compliance with the required study visits was good. A review of the drug accountability log, comparing it to the shipping records and individual subject's records found no discrepancies. There was no under-reporting of adverse events noted. The co-primary efficacy endpoints were verifiable.

At the conclusion of the study, subjects chose to continue on to the Open Label Extension Study, sponsored by Amgen, under Protocol 20120138.

At the conclusion of the inspection for Site 1-65YIRL (66080), a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the investigational plan.

Specifically, for Protocol 20110115, the investigational product (IP) was to be administered after vital signs, ECG and blood draw procedures. Subject 11566080046 on Visit Day 1 received the IP before the ECG was performed.

Dr. Awasty sent a written response to the Form FDA-483 item on November 12, 2014 and it is considered adequate. The finding was isolated and has no major safety impact.

For **Site 1-59VDW6 (66002)**, there were 18 subjects screened, 13 subjects enrolled and 12 subjects completed the study. The IRB of record was [REDACTED] (b) (4). All approvals were in order. The first subject signed the informed consent on February 6, 2013. After the conclusion of the inspection, while identifying exhibits, it was discovered that the updated consent form containing the new PI information for Subject 015 was missing page 12; contact with the site confirmed that this page was also missing from

the subject's file.

All subjects enrolled appeared to have met inclusion/exclusion criteria. The subject records contained adequate information about each subject's exposure to the test article, as well as observations and data of their condition throughout their participation in the study. Overall, individual subject compliance with the required study visits was good. There was no under-reporting of adverse events noted. The co-primary efficacy endpoints were verifiable.

At the conclusion of the study, subjects chose to continue on to the Open Label Extension Study, sponsored by Amgen, under Protocol 20120138. Dr. Looby was initially the PI for the Open Label Extension Protocol 20120138. Upon his departure, subjects were transferred to Dr. Isam Tabbah.

At the conclusion of the inspection of Site 1-59VDW6 (66002), a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. An investigation was not conducted in accordance with the investigational plan.

Specifically, for Protocol 20110115, blood pressure was to be initially recorded in both arms, with the higher reading arm being used throughout the rest of the study. Twelve of 13 subjects enrolled had only one blood pressure reading recorded at screening.

Dr. Awasty sent a written response to the Form FDA-483 item on November 12, 2014 and it is considered adequate. The finding was isolated and has no major safety impact.

- c. Assessment of data integrity:** The full Establishment Inspection Reports (EIRs) were submitted for review. Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from these two sites appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

2. Michael Bolognese
10215 Fernwood Road
Suite 40
Bethesda, MD 20817

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), institutional review board (IRB) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. For

Protocol 20110109, 35 subject records were reviewed. For Protocol 20110114, 22 subject records were reviewed.

- b. General observations/commentary:** For Protocol 20110109, there were 48 subjects screened, 35 subjects enrolled, and 35 subjects who completed the study. For Protocol 20110114, there were 49 subjects screened, 24 subjects enrolled, and 22 subjects who completed the study.

The study records were well organized and complete. The IRB of record was the central [REDACTED] ^{(b) (4)}. All subjects were appropriately consented with the current informed consent form and with the revised consent forms when they were approved by the IRB. All IRB approvals were obtained. There was incomplete documentation that subjects who speak only Spanish had a translator during consenting and visits. There was a Spanish-speaking Study Coordinator, but subject records did not always identify that she was present.

There was no under-reporting of adverse events noted. The primary efficacy endpoint for both studies was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

- 3. Tomas Hala**
CCBR Pardubice
Trida Miru 2800
Pardubice 530 02
Czech Republic

- a. What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, training records, and adverse event reports. For Protocol 20110109, 26 subject records were reviewed. For Protocol 20110115, 25 subject records were reviewed.

- b. General observations/commentary:** For Protocol **20110109**, there were 122 subjects screened, 42 subjects randomized and 34 subjects who completed the study. The first subject signed the informed consent March 1, 2012 and was

randomized and dosed April 13, 2012. The last subject completed the study July 19, 2013.

The Clinical Trial was approved in the Czech Republic by the regulatory agency January 6, 2012 and by the Multicentre Ethics Committee on January 11, 2012. All subjects had been consented but there were several minor issues noted regarding the informed consent documents (such as a subject dating the informed consent form with their birth date, consents missing the check off if the subject wanted their private physician to be made aware of their participation in the study or not).

The site used paper source records. There were also study-specific worksheets and checklists. In general, the records were legible, organized and complete.

The LDL-C at baseline and Week 52 (for primary endpoint) were compared to the sponsor line listings and there were no discrepancies. The LDL-C at baseline and Week 12 (for secondary endpoint), total cholesterol at baseline, Week 12 and Week 52 (for secondary endpoint), triglycerides at baseline and Week 52 (for secondary endpoint) and ApoB at baseline and Week 52 (for secondary endpoint) were compared to the sponsor line listings and there were no discrepancies. There was no under-reporting of adverse events noted.

For Protocol **20110115**, 54 subjects were screened, 28 subjects were enrolled, 25 were randomized, and 19 completed the study. The first subject signed their Informed Consent on April 8, 2013. There were no issues noted with the consent forms.

Primary and secondary efficacy endpoint data was verifiable. There were two instances where the physical exam changed but no adverse event was reported. It was unclear if the physical exam actually changed or was not properly documented. For Subject 016, the physical exam performed on April 16, 2013 noted the skin was normal, but on August 29, 2013, swollen legs were noted. There was no adverse event recorded in the subject file or in the line listings. For Subject 019, the physical exam performed on April 17, 2013 noted the skin was normal, but on subsequent exams on August 12, 2013 and August 28, 2013, limited movement of the shoulder was noted. There was no adverse event recorded in the subject file or in the line listings.

There were no reports of any device complaints (for auto injectors) and there were no medical device complaints within the study subject files during the inspections.

For both studies, the inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted

data.

4. Annesofie Krogsaa
Ballerup Byvej 222
Center for Clinical and Basic Research
Ballerup 2750
Denmark*

* Post-inspection correspondence should be directed to Dr. Line Markdanner Lindgren as Dr. Krogsaa is no longer employed by the firm.

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. For Protocol 20110109, 33 subject records were reviewed. For Protocol 20110114, 56 subject records were reviewed. For Protocol 20110115, 50 subject records were reviewed.
- b. **General observations/commentary:** The original principal investigator for all three studies was Dr. Pernille Lundquist. Reportedly, Dr. Lundquist left the firm on May 1, 2012. Dr. Krogsaa became PI for all three studies from April 30, 2012 and remained until the closing of the last study (December 2014). Dr. Krogsaa was not available at the inspection because she stopped working for the clinical site. The Scientific Ethics Committee in the Capital Region in Hillerod, Denmark was the regional committee and the Sundhedssyrelsen (Danish Health and Medicines Authority) in Copenhagen, Denmark was the country committee.

For **Protocol 20110109**, there were 105 subjects screened and 33 subjects enrolled into the study. Informed consent was appropriately obtained for each subject, according to regulations. The first consent form was signed on March 19, 2012 and the first subject was randomized on May 2, 2012. The last subject completed the study on June 20, 2013.

Source documents were well organized, complete, in good condition and legible. Subjects met study eligibility criteria. Protocol-specified blinding and randomization procedures were followed. Test article accountability/disposition was adequately documented.

Source documents and case report forms (CRFs) were consistent with the data listings for the primary efficacy endpoint and secondary efficacy endpoints. There was no evidence of under-reporting of adverse events.

For **Protocol 20110114**, there were 92 subjects screened and 56 subjects randomized into the study. Informed consent was appropriately obtained for each subject, according to regulations.

Subjects 015, 029, 046, 048, 051, 063, 077, 088 and 090 had complaints related to the auto injectors that were not reported to the Sponsor at the time of the complaint. All were submitted to the sponsor during the inspection.

The accountability of the ezetimibe/placebo dispensed during the study was not accurate. At the conclusion of the study, there were 77 tablets that could not be reconciled. Ezetimibe was dispensed in greater than required amounts to subjects; for example, if a subject would be returning to the clinic in 38 days, two boxes of 36 would be dispensed to the subject to cover that time period. Upon return, the subject did not always bring the unused portion to be reconciled. The reconciliation would be either delayed or estimated by the patient.

Source documents and case report forms (CRFs) were consistent with the data listings for the primary efficacy endpoint and secondary efficacy endpoints. There was no evidence of under-reporting of adverse events.

For Protocol **20110115**, there were 113 subjects screened and 50 randomized. The first subject signed informed consent on April 15, 2013. Informed consent was appropriately obtained for each subject, according to regulations.

There were four subjects in Study 20110115 (Subjects 087, 090, 092, and 109) who were randomized to the incorrect background statin therapy group (none, non-intensive, intensive). The IVRS stratification factor is used as a covariate in the analysis. Prior to signing informed consent, Subjects 087, 090, 092, and 109 were taking Simvastatin 40 mg, which per the protocol in Appendix E is considered non-intensive therapy. The subjects were wrongly enrolled in statin therapy by the study coordinator as entering under intensive statin usage. The source document titled "Statin Therapy Enrollment" was checked "Intensive statin use" but was changed to "Non-intensive statin use" by one of the sub-investigators. The Study Coordinator emailed IVRS and attempted to fix the entry statin group and was told it could not be changed because it affected randomization. A note was made in the progress notes of each subject stating the subject was randomized using the incorrect statin entry usage. During the inspection it was confirmed that a summary table showing the difference between IVRS entered values and actual values for the prior statin usage had been reported in the clinical study report.

Subjects 039, 046, 040, and 061 had complaints related to the auto injectors that were not reported to the Sponsor at the time of the complaint. All were submitted to the sponsor during the inspection.

Source documents and case report forms (CRFs) were consistent with the data listings for the primary efficacy endpoint and secondary efficacy endpoints. There was no evidence of under-reporting of adverse events.

For all three studies, the inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

- 5. Ben Lasko
Manna Research Incorporated
2291 Kipling Avenue
Unit 117B
Toronto, ON M9W 4L6
Canada*

*Dr. Lasko retired October 2014. Manna Research Incorporated provided a representative (former Sub-Investigator (b)(4)) to assist during the inspection. In addition, the site moved into a new facility in July 2014. The address and unit number remain the same but actual facilities used during the conduct of Protocols 20110109 and 20110114 were not available. Post-inspectional correspondence should be addressed to Manna Research, Inc. c/o Carrie Lahti.

- a. **What was inspected:** The inspection focused on 100% review of informed consent documents (ICDs), ethics committee (EC) correspondences, 1572s, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. For Protocol 20110109, there were 59 screen failure subject records reviewed and 32 enrolled subject records reviewed. For Protocol 20110114, all 29 subject records were reviewed.
- b. **General observations/commentary:** For Protocol **20110109**, there were 100 subjects screened, 41 subjects enrolled into the study and 28 subjects who completed the study. The first subject was administered test article March 9, 2012. Informed consent was appropriately obtained for each subject according to regulations except Subject 099 signed an outdated copy of the consent form.

Review of study records found that the protocol appeared to be followed properly by staff participating in this study. All protocol deviations appeared to

have been reported. Procedures for randomization were followed appropriately. Review of data listings for the primary efficacy endpoint and secondary efficacy endpoints verified consistency with the source records. There were two adverse events noted to not be reported on the line listings: Subject 005 Diarrhea (January 10-11, 2013) and Subject 037 Stomach Flu (December 27-29, 2013).

There were disorganized entries in the investigational product accountability logs; numerous duplicate entries, late entries, dispensed IP not administered and added back to the log. This was seen more at the beginning of the study. Management had the reconciliations done more often and the accountability records improved.

For Protocol **20110114**, there were 29 subjects screened, 14 subjects enrolled into the study and 10 subjects who completed the study. The first subject was administered test article March 20, 2013. Informed consent was appropriately obtained for each subject according to regulations.

Review of study records found that the protocol appeared to be followed properly by staff participating in this study. All protocol deviations appeared to have been reported. Procedures for randomization were followed appropriately. Review of data listings for the primary efficacy endpoint and secondary efficacy endpoints verified consistency with the source records. There was no under-reporting of adverse events. Records regarding reconciliation of the test articles and records for dispensing appeared adequate and there were no apparent discrepancies noted.

There were nine auto-injector Prefilled Syringe (PFS) complaints documented. Subject 1026 had two separate syringes consecutively malfunction. Review of the Investigational Product Instruction Manual did not provide guidance if more than one syringe malfunctioned at one time. Therefore, staff recorded both malfunctions on one complaint form.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this site appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

- 6. Amgen, Inc.
ATTEN: Robert A. Bradway, CEO
One Amgen Center Drive
Mail Stop 17-2-B
Thousand Oaks, CA 91320-1799

- a. What was inspected:** The inspection focused on IRB approvals, the Global Informed Consent Template forms (with ClinTrials.gov wording) and all changes, 1572s, financial disclosures, site selection, organization personnel, training records, CVs and licenses, monitoring reports, Standard Operating Procedures (SOPs), contracts, the Framingham Risk Score procedures, the Data Monitoring Committee (DMC) membership selection process, DMC charter, sponsor interactions, device complaint process, device complaint database, safety reporting, site trial master files, study trial master files, regulatory communications, records retention, test article disposition, data management, and the Interactive Voice Response System (IVRS).
- b. General observations/commentary:** In 2008, Amgen moved to the Functional Service Provider (FSP) model and maintains multiple vendors globally. The study management team of Amgen selected (b) (4) as the central IRB for all three studies. Amgen contracted (b) (4) as the contracted safety supplier for all three studies. Amgen used a third party for electronic data capture and eCRF management. Amgen did the monitoring for Study 20110115.

Clinical trial oversight for all three studies appeared to be adequate. All records were available for inspection. All safety reports appeared to be submitted in a timely manner. Amgen's Global Safety Team performs a review of aggregate data for adverse events, serious adverse events, and adverse events of interest for signal detection/trending. If a positive safety signal is detected, a cross functional team is pulled together to discuss the safety risks.

Review of the complaint/CAPA system indicated that there were no product complaints that resulted in CAPAs for the three studies reviewed. The complaint data for Protocols 20110114 and 20110115 were reviewed. There were (b) (4) auto-injectors distributed and (b) (4) complaints. Most complaints were related to activation difficulty. Amgen investigated each of these complaints and determined that the majority were related to not properly following the injection administration procedure outlined in the instructions given to each subject.

One ineligible subject was enrolled into Protocol 20110114 because the site (Bolognese Site 1-51Q [66402]) calculated the Framingham Risk Score incorrectly (Subject 4042). This error was evaluated. The preferred and recommended Framingham Risk Score assessment tool for the trial was the official NCEP calculator. The calculator was available by the sponsor via a link and a downloadable spreadsheet in the event that the official website was not available. The Bolognese site used the website calculator; the site inserted the wrong blood pressure. The site monitors were required to confirm the Framingham Risk Score for enrolled subjects.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

- c. **Assessment of data integrity:** The full Establishment Inspection Report (EIR) was submitted for review. Data from this sponsor appear acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this BLA consisted of two domestic and three foreign clinical sites, representing 10 protocol sites for the three studies, as well as the Sponsor.

Observations noted above for all sites and the Sponsor are based on the preliminary review of the Establishment Inspection Reports.

One clinical site inspected, Dr. Awasty, representing two protocol sites for a single study (Study 20110115), was issued a Form FDA-483, citing inspectional observations. Classification for this site is Voluntary Action Indicated (VAI). Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this site is acceptable for use in support of the indication for this application.

The Sponsor Amgen and Drs. Bolognese, Hala, Krogsaa and Lasko were not issued a Form FDA 483; the classifications are all NAI (No Action Indicated). Data from these sites and the Sponsor are considered reliable based on the available information.

In general, based on the inspections of the five clinical sites (representing 10 protocol sites) and the Sponsor, the inspectional findings support validity of data as reported by the Sponsor under this BLA.

{See appended electronic signature page}

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

/s/

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KASSA AYALEW
05/05/2015

LABEL AND LABELING 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: April 13, 2015

Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)

Application Type and Number: BLA 125522

Product Name and Strength: Repatha (evolocumab) Injection, 140 mg/mL [Prefilled Syringe]
Repatha SureClick (evolocumab) Injection, 140 mg/mL [Autoinjector]

Product Type: Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: Amgen

Submission Date: August 27, 2014

OSE RCM #: 2014-1869

DMEPA Primary Reviewer: Mishale Mistry, PharmD, MPH

DMEPA Team Leader: Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the results of the Human Factors Study (HFS), container label, carton labeling, Prescribing Information, Instructions for Use, and Reference Guide for Repatha (evolocumab) injection, 140 mg/mL (prefilled syringe) and Repatha SureClick (evolocumab) injection 140 mg/mL (prefilled pen), BLA 125522, submitted on August 27, 2014. The Division of Metabolism and Endocrinology requested that DMEPA review the HFS study results, and proposed labels and labeling for areas of vulnerability that may lead to medication errors.

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
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C
Human Factors Study	D
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 Human Factors Study

Repatha (Prefilled Syringe-PFS)

Based upon the results of the Human Factors Study, the prefilled syringe appears to be safe and effective when used by patients, caregivers, and healthcare professionals who have training materials (Instructions for Use) available for review.

With regard to the methodology of the Human Factors Study for PFS, DMEPA notes a flaw in that prior to administering the first testing scenario, the moderator requested that all participants read through the IFU, which we believe represents training (i.e., self-training). However, if the Applicant's intention was to include a participant arm with no training, the participants in this arm should not be prompted to review the IFU. However, in the actual use environment, we expect that this patient population will typically receive training from their health care providers prior to use because it is likely that this patient population is injection-naïve since there are currently no marketed injectable therapies for this indication (primary

hyperlipidemia, mixed dyslipidemia, homozygous familial hypercholesterolemia). Thus, we find the methodology regarding training acceptable.

With regard to the results of the Human Factors Study, 81 failures occurred during the study as follows:

- 62 failures in Session 1 (introductory session during which participants were directed towards reading an IFU and simulated their first injection): 29 patient participants, 21 caregiver participants, 12 healthcare provider participants
- 19 failures in Session 2 (session held approximately one week later to assess learning and memory decay): 7 patient participants, 9 caregiver participants, 3 healthcare provider participants

Failures occurred within the following tasks of the study:

1. Store the device properly
2. Wait 30 minutes for the drug to reach room temperature
3. Wash hands thoroughly
4. Clean the injection site with an alcohol wipe
5. Open the packaging/outer carton (operational difficulty)
6. Check product expiration date
7. Create a skin platform (i.e., pinch a skin pad)
8. Depress the syringe plunger to deliver a complete dose
9. Examine the injection site following the injection

Failures to wash hands thoroughly, clean the injection site, open the packaging/outer carton, and examine the injection site:

- Errors 3, 4, and 9 (wash hands thoroughly, clean the injection site with an alcohol wipe, and examine injection site) are not associated with the device-user interface of the product, but rather with other aspects of product use and are not unique to this injectable device. Therefore, these errors do not affect the results of the study in terms of the safe and effective use of the prefilled syringe.
- In Error 5, participants experienced operational difficulties with opening the outer carton, but were successful in removing the device from its packaging. Such difficulties may result in delay of treatment but do not affect the results of the study in terms of the safe and effective use of the prefilled syringe.

Failure to store device properly:

Errors associated with the failure to store the device properly occurred with two caregiver participants. One caregiver said the device should be stored in a cool dry place, and the other caregiver said he wasn't sure, and suggested a cupboard. We may attribute this error to perceptual failures as both caregivers reported that they did not see this information in the proposed IFU. The proposed IFU states in the section titled "Important" that ^{(b) (4)} Repatha prefilled syringe ^{(b) (4)} in the refrigerator between 2 °C to 8 °C (36 °F to 46 °F)." Additionally, the proposed carton labeling and syringe tray labeling includes storage

information. However, we recommend that the Sponsor increase the prominence and readability of this information in the proposed IFU and mitigate this type of error.

Failure to wait 30 minutes for drug to reach room temperature:

Failure to wait 30 minutes for the drug to reach room temperature occurred among 10 participants (patients, caregivers, and healthcare providers). We may attribute this error to both perceptual failures and participant forgetfulness as five participants said they did not see this information in the IFU and five participants said they remembered reading the information, but they forgot to mention they would wait while giving the injection. This type of error may result in uncomfortable injections and underdosing as end users may have difficulty delivering the complete injection (b) (4). The proposed IFU states in Step 1A to “wait at least 30 minutes for the prefilled syringe in the carton to (b) (4) reach room temperature before injecting.” Thus, we recommend that the Sponsor increase the prominence of this information in the proposed IFU and explain the importance of waiting the recommended amount of time before delivering the injection, in order to mitigate this type of error.

Failures to check product’s expiration date, inspect drug appearance, and inspect the device:

Errors associated with failure to check the product’s expiration date (21 failure), inspect the drug’s appearance (ten failures), and inspect the device (six failures) for damage occurred among patient, caregiver and healthcare provider participants. We may attribute these errors to perceptual failures as participants reported that they did not see these steps on the IFU. On the proposed IFU, Step 1B states “DO NOT use if (b) (4) date (b) (4) has passed” and Step 1F instructs users to not use the prefilled syringe if “the expiration date (b) (4) has passed”. However, we recommend that the Sponsor increase the readability of these steps to mitigate these types of errors.

Failure to create a skin platform:

Failure to create a skin platform (i.e., pinch the skin pad) occurred among seven patients and caregivers (four cases of failure in Session 1 and three cases of failure in Session 2). We may attribute some of these errors to participant forgetfulness as three participants said they remembered reading this instruction, but forgot in the moment. One of the failures is an artifact as the participant had an underlying health condition and could only use one hand; and thus was unable to pinch the skin pad. Another failure can be attributed to the participant’s pre-existing notions as the participant did not think the skin pad could be pinched, which also represents an artifact of the study. However, one participant believed pinching was only necessary if injecting into the belly, as is shown in the figure in Step 2 (b) (4) of the proposed IFU. Therefore, recommendations can be made for the Sponsor to increase the readability of this step to clarify that end users should pinch the skin to create a firm surface, regardless of the injection site.

Failure to depress skin plunger to deliver a complete dose:

Failure to depress the syringe plunger to deliver a complete dose on the first attempt occurred in five cases, among two patients and one caregiver participant. One of the cases of failure in a patient during Session 2 can be attributed to the participant’s inaccurate perception that the

injection had completed. She removed the syringe prematurely, explaining she felt resistance on the syringe, which led her to believe the injection was complete.

One of the patient participants did not have self-injection experience and had paralysis in left arm and leg due to a stroke several years prior to participation in the study. In the first session, the participant unintentionally pulled the needle out of the skin pad while giving the injection, squirting medicine onto the skin pad. After briefly pulling the needle out prematurely, the participant re-inserted the needle. The participant reported that she felt the skin pad had more resistance than normal skin. For the second injection attempt, the moderator did not pinch the skin pad. Again, the needle came out and medicine squirted onto the skin pad. The moderator commented that the patient did not have the needle fully inserted into the skin pad. When asked if she would fully insert the needle if performing the injection into real skin, the participant said yes. In the participant's second session, the participant failed to deliver a full dose of medication before removing the needle from the skin pad. As occurred in the first week, the participant unintentionally pulled the needle out of the skin pad before completing the injection. Again the participant commented that she felt resistance on the plunger. The participant injected at 45 degrees, and thought the shallow angle contributed to her failure. She was given a second attempt, and successfully delivered a complete injection at a 90 degree angle.

During the first session, an injection-naïve caregiver thought that he needed to perform the injection into a vein (despite reading the IFU) and inserted the needle at a very acute angle. The participant applied pressure to the plunger rod for approximately 1 minute with no medication going into the skin. Researchers believed that the participant did not push the needle tip entirely through the rubber exterior, making it impossible to push the liquid out of the syringe. The participant was given a second attempt at giving the injection, and the moderator suggested that the participant inject at a less shallow angle. The participant successfully delivered a full dose of medication on his second attempt. During the second session, the participant failed to deliver a complete injection on first attempt. He reported that he did not know how far to insert the needle because he did not want to hit the bone or hurt the patient. On his second attempt, the participant successfully delivered a full dose of the medication. These errors can be attributed to the participant's preconceived notions and can be considered an artifact of the study.

Failure to deliver a complete dose occurred because participants removed the syringe prematurely. According to the Sponsor, in four of the five cases of failure, the participant was able to expel at least half of the dose. Missed or partial dosing as a result of removing the syringe prematurely is considered acceptable given the low severity of the anticipated clinical effect. However, chronic underdosing may occur if the error occurs consistently during multiple injections, which would result in decreased efficacy of the product, given the infrequent administration of Repatha. The three participants were able to deliver a complete dose at least once in the study, indicating that they were able to apply the force required to complete a dose. Additionally, the Sponsor mentions that a simulated injection into the rubber layer of the skin pad resulted in high resistance to dose completion, which would not occur when injecting into subcutaneous tissue.

In the currently proposed IFU, Step 3B states in bold text, “Using slow and constant pressure, PUSH the plunger rod all the way down until the syringe is empty.” Due to the errors seen in delivering a complete dose, we recommend that the Sponsor emphasize that (b) (4) end users may experience resistance when pushing down on the plunger rod and injection time may be longer than most medications administered subcutaneously, but they must continue to push down until the syringe is empty and the complete dose is delivered.

Recommendations to improve the IFU in terms of the readability and prominence of important information may mitigate the errors seen in this study. The failures encountered in this study have also been reported with the use of similar, currently marketed, prefilled syringes and therefore, we do not believe that the risks present a safety concern.

Repatha SureClick (Prefilled Pen/Autoinjector)

Based upon the results of the Human Factors Study, the prefilled pen/autoinjector appears to be safe and effective when used by patients, caregivers, and healthcare professionals who receive training (i.e., introduction to the device and injection process) and/or have training materials (Instructions for Use) available for review. With regard to the results of the Human Factors Study, 39 failures occurred during the study:

1. 7 failures associated with selecting the wrong injection site
2. 2 failures associated with removing the orange cap of the autoinjector
3. 20 failures associated with activating the autoinjector by pushing firmly on the injection site and pressing the grey button
4. 10 errors associated with holding the autoinjector against the skin until the injection is complete.

A larger number of untrained participants failed to correctly perform the simulated injection than trained participants. According to the Sponsor, 50% of untrained participants failed the injection whereas 21% of trained participants failed. Thus, it appears that patient and caregiver training regarding how to use device correctly appears to improve the correct use of the product. As a result, we recommend including statement regarding needed training in the PI and IFU labeling.

Failure to select the correct injection site:

Errors associated with selecting the wrong injection site occurred during the first session. 4 patients (1 trained, 3 untrained) self-injected into the arm and 3 untrained caregivers placed the injection pad on the mannequin’s forearm. Of the untrained participants, all used some form of instructional material. Some participants perceived upper arm to be a common injection site, and noted that the arm was listed as a recommended injection site in the IFU. Another participant chose upper arm as an injection site based on previous experience of receiving injections into upper arm or self-injections administered into the upper arm, and also noted that the arm was listed as a recommended injection site in the IFU. These participants did not see the information in the IFU about the arm as an injection site for injections delivered

by someone else during the training. Another participant selected the forearm as an injection site for easy access to a vein with the belief that the medication was to be delivered in a vein based on previous experience of receiving injections. One participant, who reported not reading the instructions carefully enough, assumed it would be difficult to maneuver the injection pad around the mannequin's upper arm and selected the forearm for convenience. Another participant selected forearm as injection site based on previous experience of self-injections. We can attribute some of these errors to the participants' preconceived beliefs and previous experience with injections (among the injection-experienced participants). With regard to the proposed IFU, Step 1D states that (b) (4) can use...outer area of upper arm ((b) (4) if someone else is giving you the injection)." However, we recommend that the Sponsor increase the prominence of this information in the proposed IFU to mitigate these types of errors.

Failure to remove the orange cap of the autoinjector:

Failure to remove the orange cap off of the autoinjector occurred among one untrained patient and one trained caregiver. One participant failed to read the reference guide thoroughly and missed information about removing the orange cap off and another participant did not realize that there was more information on Side 2 of the Reference Guide and therefore did not see the instructions on removing the orange cap. Side 1 of the Reference Guide provides an arrow titled "turn over to continue..." to direct users to look at Side 2, which includes an image demonstrating a user pulling off the orange cap, with a caption stating "pull orange cap straight off". Additionally, Step 2A of the proposed IFU instructs users to "pull the orange cap straight off when you are ready to inject" and also provides a visual image of the action. Therefore, no additional modifications to the Reference Guide or proposed IFU are needed to mitigate this type of error.

Failure to activate the autoinjector:

Failure to activate the autoinjector by pushing down firmly on injection site and pressing grey button occurred in 20 cases, in which 16 cases occurred in the first session, demonstrating that this behavior may be an exhibition of one-time learning. Eleven of these failures occurred among untrained participants (3 patients, 3 caregivers, and 5 healthcare providers) and 9 failures occurred among trained participants (1 patient, 3 caregivers and 5 healthcare providers).

We can attribute some of these errors to pre-existing notions of the participants. One participant approached the injection process as an "easy" and simple process, and did not anticipate the amount of pressure needed to trigger the device. Another participant heard a soft click when pressing the grey button, misinterpreting the sound as a signal that the device was activated and the injection started. One participant misinterpreted a 90 degree placement of the device as a slight angle (45 degrees), and was unable to depress the safety guard and trigger the device. Additionally, a participant believed that the orange cap covered the "plunger", which once removed, would reveal the functional piece of the device.

Given the participants' previous experience with other autoinjectors, we can attribute some of the errors to negative transfer. Some participants applied the same amount of pressure on this device as with other autoinjector devices and/or syringes used in the past, but the pressure applied was not sufficient to trigger the device and initiate the injection. Other participants

expected to see a needle after removing the orange cap, based on previous experiences with other injection devices (syringes). One participant did not understand the order of the steps to activate the device and placed the device against the injection site (without applying enough pressure), and expected to press down on the grey button immediately (pressing the device down and pushing the grey button simultaneously locks the device and makes activation impossible).

We can attribute some errors to the proposed IFU as participants noted that the instructions did not specify how “deep” the autoinjector had to go into the skin to trigger the device, but rather just stated to press the device “firmly”. Another participant noted that participant interpreted instructions to mean that end-users need to depress the grey “start” button firmly, rather than the yellow needle shield, to activate the device and push the needle down. One participant did not see the smaller image of “pushing down” the device, stating that the image was buried within the instructions of Step 3B and did not raise attention. Finally, another participant noted no indication in instructions to where the needle is located in the device.

In one case, the user did not expect the amount of pressure needed to activate the device. Therefore, we may attribute the error to inexperience with injections.

Failure to activate the autoinjector by pushing down firmly on injection site and pressing grey button would result delay of treatment. With regard to the proposed IFU, Step 3A provides a diagram of the autoinjector placed on the injection site at a 90 degree angle with related instructions. Step 3B instructs users to “firmly push down autoinjector onto skin until it stops moving...you must push all the way down but do not touch the gray button until you are ready to inject.” .” Although some of these errors can be considered an artifact of the study, due to the errors associated with these steps in the study and potential resulting delay of treatment, we recommend that the Sponsor increase the prominence of this information in the proposed IFU and emphasize the force required to activate the autoinjector (b) (4) to mitigate these types of errors.

Failure to hold the autoinjector against the skin until the injection is complete:

Errors associated with holding the autoinjector against the skin until injection is complete occurred in 10 cases, of which nine occurred in the first session. Six of the errors occurred in untrained participants, whereas 4 errors occurred in the trained participants.

We may attribute one of the failures to a participant’s preconceived notions as they expected the device to deliver the medication immediately due to the “modern” look of the device. We may attribute other errors to participants’ previous experience with other autoinjectors. One participant believed from past experience that the injection would initiate when the yellow needle shield was depressed, and did not press the grey button. Other participants heard a soft click, which they interpreted as the completion of the injection. Additionally, another participant did not hold the device in place for long enough based upon previous experience with other autoinjectors. Because a participant did not know how long to wait for the injection to be complete, we may attribute this error to the participant’s unfamiliarity with injections.

Finally, some participants forgot to wait for 15 seconds after the click and to watch the window turn yellow during the injection. Another participant believed that the testing session was a test of memory and did not refer to any instructional material. We may consider these errors as artifacts of the study attributed to participant forgetfulness.

As discussed above, all 10 participants prematurely lifted the activated autoinjector, thus experiencing a wet injection, resulting in an incomplete dose delivery. According to the Sponsor, once activated, the autoinjector continues to deliver the dose, even if prematurely lifted. Therefore, it was difficult to gauge how much of the dose was actually delivered. Missed or partial dosing as a result of removing the autoinjector prematurely is considered acceptable given the low severity of the anticipated clinical effect. However, chronic underdosing may occur if the error occurs consistently during multiple injections, which would result in decreased efficacy of the product, given the infrequent administration of Repatha SureClick. The risk of overdose is less concerning as end users will be fully aware if they did not deliver the complete dose because the autoinjector continues to deliver the dose once activated. All 10 participants who experienced a wet injection in the study were asked to perform a second injection immediately afterwards and successfully completed the injection. This suggests that the failure is not a repeatable use error. Additionally, none of the participants who experienced a wet injection on their first visit experienced another wet injection on their second visit one week later, which further supports the belief that the error is attributable to a learning effect. Furthermore, in a Phase 1 clinical trial, complete delivery of evolocumab was observed for 98.9% (430/435) of the autoinjectors used.

In the currently proposed IFU, Step 3D states in bold text, “Keep pushing down on skin. Then lift thumb. Your injection could take about 15 seconds.” Due to the errors seen in delivering a complete dose, we recommend that the Sponsor modify the proposed IFU to place greater emphasis on the visual and auditory signs (end users can see the window change from white to yellow and may hear a second click) that indicate to the end user when the injection is complete. Additionally, we recommend that the Sponsor emphasize that (b) (4), injection time may be longer than most medications administered subcutaneously.

Recommendations to improve the IFU in terms of the readability and prominence of important information may mitigate the errors seen in this study. The failures encountered in this study have also been reported with the use of similar, currently marketed, prefilled autoinjectors. Additionally, the proposed Repatha SureClick autoinjector is a modified version of the SureClick autoinjector currently approved for Enbrel (etanercept). The proposed autoinjector differs from the SureClick autoinjector in color, (b) (4). The failures encountered in this study are consistent with those reported with the Enbrel SureClick autoinjector and therefore, we do not believe that the risks present a safety concern.

3.2 Repatha and Repatha SureClick 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 noted that the container labels, carton labeling, Prescribing

Information, and Instructions for Use for both Repatha and Repatha SureClick can be improved to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information.

In summary, DMEPA expects that patients, caregivers, and health care professionals will be able to use Repatha prefilled syringe and Repatha SureClick autoinjector safely and effectively when training is provided and/or training materials (i.e., Instructions for Use and/or Reference Guide) are available for review.

4 CONCLUSION & RECOMMENDATIONS

The Human Factors studies for Repatha prefilled syringe and Repatha SureClick autoinjector demonstrated that end users (patients, caregivers, and health care professionals) are able to use the product safely and effectively when used with the availability of formal training and/or training materials (i.e., Instructions for Use).

Additionally, the proposed labels and labeling can be improved to increase the readability and prominence of important information, to promote the safe and effective use of the product, to mitigate any confusion, and to clarify information.

4.1 RECOMMENDATIONS FOR THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this BLA:

A. We recommend changing any reference to “single-use” prefilled syringe or prefilled pen in the Prescribing Information labeling to “single dose” to ensure that the entire dose is delivered and the injectable device is not reused.

B. Highlights of Prescribing Information

1. Dosage Forms and Strengths

- i. Revise (b) (4) to ‘140 mg/mL Repatha Single-Dose Prefilled Syringe’ concentration statement in accordance with USP General Chapter <1>.
- ii. Revise ‘ (b) (4), to ‘140 mg/mL mg Repatha Single-Dose Prefilled Repatha SureClick Autoinjector’ concentration statement in accordance with USP General Chapter <1>.
- iii. Recommend removing the statements (b) (4) ” as this information is repetitive and is located in Section 16.

C. Full Prescribing Information

1. Section 2 Dosage and Administration

- i. (b) (4)

ii. [Redacted] (b) (4)

[Redacted] (b) (4)

iii. [Redacted] (b) (4)

iv. [Redacted] (b) (4)

2. Section 3 Dosage Forms and Strengths

- i. Revise '[Redacted] (b) (4)' to '140 mg/mL Repatha Single-Dose Prefilled Syringe' concentration statement in accordance with USP General Chapter <1>.
- ii. Revise '[Redacted] (b) (4)', to '140 mg/mL mg Repatha Single-Dose Prefilled Repatha SureClick Autoinjector' concentration statement in accordance with USP General Chapter <1>.
- iii. Recommend removing the statements "[Redacted] (b) (4)" as this information is repetitive and is located in Section 16.

3. Section 16 How Supplied/Storage and Handling

- i. Revise the '[Redacted] (b) (4)' concentration statement to '140 mg/mL' in accordance with USP General Chapter <1>.

4. Section 17 Patient Counseling

- i. Include the following statement to ensure that patients/caregivers receive training and are aware of the longer than usual injection time:

[Redacted text block containing a statement, with a (b) (4) label in the top right corner.]

4.2 RECOMMENDATIONS FOR AMGEN

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

Instructions for Use:

- A. We recommend changing any reference to “single-use” prefilled syringe or prefilled SureClick Autoinjector in the Instructions for Use labeling to “single dose” to ensure that the entire dose is delivered and the injectable device is not reused.

B. Repatha Prefilled Syringe

- 1. Under the section titled “Important”, we recommend to:
 - i. Include a subsection that discusses statements related to the storage of Repatha, to mitigate the errors seen in the Human Factors study, so that end users do not overlook this information.
 - ii. Include complete storage instructions if Repatha is removed from the refrigerator, as mentioned in Section 16 of the Prescribing Information labeling.
 - iii. Revise the statement “Do not freeze the Repatha prefilled syringe or use (b) (4) that has been frozen.” to “Avoid freezing the Repatha prefilled syringe or using one that has been frozen.” as the negation “NOT” can be overlooked.¹
 - iv. Revise the statement (b) (4) ” to include the importance of caregivers also receiving training prior to administering an injection. Suggested language may include: “It is important that you do not try to give yourself *or someone else* the injection...”

For example:

¹ Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

IMPORTANT

Before you use a Single-Dose Repatha Prefilled Syringe, read this important information:

- It is important that you do not try to give yourself or someone else the injection unless you have received training from your healthcare provider.
- The grey needle cap on the Repatha prefilled syringe (b) (4) dry natural rubber, which is made from latex. Tell your healthcare provider if you are allergic to latex.

Storage of Repatha:

- Keep the Repatha prefilled syringe in the original carton to protect from light during storage.
- (b) (4) in the refrigerator between 2 °C to 8 °C (36 °F to 46 °F).
- If removed from the refrigerator, Repatha prefilled syringe should be kept at room temperature (up to 25 °C (77 °F)) in the original carton and must be used within 30 days.
- (b) (4).
- Keep the Repatha prefilled syringe out of the sight and reach of children.

(...include the other important information listed in this section)

2. In Section A of “Step 1: Prepare”, we recommend to:
 - i. Explain the importance of waiting the recommended amount of time before delivering the injection, in order to mitigate the errors seen in the Human Factors study. For example, we recommend including the following statement:

(b) (4), wait at least 30 minutes for the prefilled syringe in the carton to (b) (4) reach room temperature before injecting.”
 - ii. Include an image of a clock with 30 minutes highlighted to visually emphasize this step to end users.
3. In Section B of “Step 1: Prepare”, we recommend revising the statement “DO NOT use if (b) (4) date (b) (4) has passed” to an affirmative statement, in order to mitigate the errors seen in the Human Factors study, as the negation “NOT” can be overlooked.² For example:

“Check the expiration date on your Repatha prefilled syringe carton. If the expiration date has passed, do not use the prefilled syringe.”
4. In Section F of “Step 1: Prepare”, we recommend we revising the statement (b) (4) to an affirmative statement and relocate to the “Check that...” subsection, in order to mitigate the errors seen in the Human Factors study as the negation “NOT” at the beginning of the “DO NOT” subsection can be overlooked.² For example:

“Check that...the expiration date on the prefilled syringe has not passed. If the expiration date has passed, do not use the prefilled syringe.”
5. In Section (b) (4) of “Step 2: Get ready”, we recommend changing the image of the user pinching (b) (4) to a more general image of pinched skin, in order to

² Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

mitigate the errors seen in the Human Factors study, so that end users understand that they need to pinch the skin, regardless of the selected injection site.

6. In Section B of “Step 3: Inject”, we recommend including the following statement to mitigate the errors seen in the Human Factors study, so end users understand that the resistance and long injection time may be related to the nature of the drug product:

“(b) (4), you may experience resistance and the time required for injection may be longer than most medications administered subcutaneously.”

7. We recommend removing the (b) (4) on Side 1 of the Instructions for Use labeling, as end users may not understand their meaning.

C. Repatha SureClick Prefilled Autoinjector

1. See Recommendations B.1, B.2, and B.3.
2. In Section D of “Step 1: Prepare”, we recommend rephrasing the statement “(b) (4)”, in order to mitigate the errors seen in the Human Factors study, so that end users understand that the upper arm is not used as an injection site for self-administration. For example:

“If someone else is giving you the injection, they can also use the outer area of the upper arm”
3. In Section B of “Step 3: Inject”, we recommend the following in order to mitigate the errors seen in the Human Factors study:
 - i. Include the following statement so end users understand that the increased amount of force required to activate the device may be related to the nature of the drug product:

“(b) (4) you may need to apply more downward pressure than compared to most autoinjectors.”
 - ii. Include a downward-facing arrow stemming from the hand in the main image instead of providing the smaller, embedded image to emphasize that end users need to push the autoinjector down onto the skin.
 - iii. Circle the area around the gray button in order to emphasize to users that they should not touch the gray button until they are ready to inject.
4. In Section C of “Step 3: Inject”, we recommend the following in order to mitigate the errors seen in the Human Factors study:
 - i. Include a downward-facing arrow stemming from the hand to emphasize that end users need to *continue* to push the autoinjector down onto the skin.
 - ii. Circle the area around the gray button in order to emphasize to users that they *now* press the gray start button.
5. In Section D of “Step 3: Inject”, we recommend the following in order to mitigate the errors seen in the Human Factors study:
 - i. Include a downward-facing arrow stemming from the hand to emphasize that end users need to *continue* to push the autoinjector down onto the skin.

- ii. Circle the area around the gray button in order to emphasize to users that they *now* lift their thumb off the gray button.
 - iii. Increase the size of the clock so that the injection time is more prominent.
 - iv. Including the following statement so end users understand that the long injection time may be related to the nature of the drug product:

“(b) (4) *the time required for injection may be longer than most medications administered subcutaneously.*”
 - v. Include the following statement so end users are aware of the auditory notification that their injection is complete:

“You may hear a second click when your injection is complete.”
6. Reference Guide
- i. In Step 2 (Side 2), include the image of the 90° angle (similar to that in Step 3A of the Instructions for Use).
 - ii. Revise images in Steps 2, 3 and 4 per revisions made to the Instructions for Use.
7. We recommend removing (b) (4) on Side 1 of the Instructions for Use labeling, as end users may not understand their meaning.

Container Label and Carton Labeling:

A. ALL container label and carton labeling (for Repatha and Repatha SureClick)

- 1. (b) (4)
- 2. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
- 3. Increase the prominence of the strength per 21 CFR 201.15(a)(6) by increasing the font size.
- 4. Change any reference from “single-use” to “single dose” to ensure that the entire dose is delivered and the injectable device is not reused.
- 5. Relocate the net quantity statement ‘(1 mL)’ away from the product strength and decrease its prominence as the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.⁴

³ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

⁴ (b) (4)

⁴ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from:

6. We recommend removing the symbols and replacing with text, as end users may not understand their meaning. For example:
 - i. Revise the latex symbol to the text, “This product contains dry natural rubber.”
 - ii. Revise the single use symbol to the text, “Single dose only” and list after the route of administration.
 - iii. Revise the caution symbol to the text, “See prescribing information and Instructions for Use for complete instructions.”
7. Unbold the Rx only statement as it competes in prominence with other important information on the labels and labeling.⁵

B. Immediate container labels

1. For Repatha and Repatha SureClick:

- i. See Recommendations A.1. – A.5 and A.7.
- ii. If space allows, include the route of administration and package type to identify how the drug product should be safely used and handled. For example:

“For subcutaneous use only. Single dose only.”
- iii. If space allows, we recommend removing the symbols and replacing with text, as end users may not understand their meaning. See Recommendation A.6. for suggested language.

2. Repatha Prefilled Syringe:

- i. The finished dosage form should appear on the line below the proper name. For example:

Repatha
(evolocumab)
Injection
140 mg/mL
For subcutaneous use only. Single-dose only. *(may include route of administration and packaging on prefilled syringe label if space allows)*

3. Repatha SureClick:

- i. The finished dosage form should appear on the line below the proper name. For example:

Repatha SureClick
(evolocumab)
Injection
140 mg/mL

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

“The net quantity statement should appear on the PDP but should be separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).”

⁵ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

“Other information on the PDP such as the Rx-only statement...should not compete in size and prominence with the important information listed above.”

For subcutaneous use only. Single-dose only. *(may include route of administration and packaging on prefilled syringe label if space allows)*

C. Carton labeling (including carton tray labeling)

1. For Repatha and Repatha SureClick:

- i. See Recommendations A.1. – A.7.
- ii. Revise the strength in the dark blue circle from ‘(b) (4)’ to ‘140 mg/mL’ in accordance with USP General Chapter <1>.
- iii. Relocate route of administration, to be located immediately after the strength, to increase its prominence on the Principal Display Panel.⁶ Include the package type statement, to be located immediately after the route of administration, to clearly identify how the drug product should be safely used and handled. For example:

“For subcutaneous use only. Single dose only.”
- iv. Include complete storage instructions if Repatha is removed from the refrigerator, as mentioned in Section 16 of the Prescribing Information labeling.
- v. Images should represent the actual dosage form (i.e., prefilled syringe or prefilled autoinjector) and reflect the true size and color; schematic or computer-generated images should not be used. We recommend removing the images of the prefilled syringe and prefilled autoinjector on the carton labeling (and carton tray labeling for the prefilled syringe).⁷ If an actual image of the prefilled syringe or prefilled autoinjector is used, the image should not compete in size or prominence with the proprietary name and/or established name and strength.

2. Repatha Prefilled Syringe:

- i. See Recommendation B.2.i.

3. Repatha Prefilled Autoinjector:

- i. See Recommendation B.3.i.

⁶ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

“We recommend that the PDP include the following critical information...route(s) of administration...the information listed above should be the most prominent information on the PDP.”

⁷ See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr [cited 2014 Jun 12]. Available from:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>.

“If an image is used on the PDP, the image should appear at the bottom of the label and should not compete in size or prominence with the proprietary and/or nonproprietary name and strength information. Images should...reflect the true size, color, and imprint.”

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Repatha and Repatha SureClick that Amgen submitted on August 27, 2014.

Table 2. Relevant Product Information for Repatha and Repatha SureClick	
Initial Approval Date	N/A
Active Ingredient	evolocumab
Indication	<p>Indicated as an adjunct therapy to diet to:</p> <ul style="list-style-type: none"> • Reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with hyperlipidemia or mixed dyslipidemia <ul style="list-style-type: none"> — in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or — alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or — alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate. • Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia
Route of Administration	subcutaneous injection
Dosage Form	solution for injection
Strength	140 mg/mL
Dose and Frequency	<p>Primary hyperlipidemia or mixed dyslipidemia:</p> <ul style="list-style-type: none"> • Administer 140 mg every 2 weeks, or • 420 mg once monthly in the upper arm, thigh, or the abdomen <p>Homozygous familial hypercholesterolemia:</p> <ul style="list-style-type: none"> • Administer 420 mg either once monthly or every 2 weeks. Patients on apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule
How Supplied	<p>Repatha 140 mg/mL single-use prefilled syringe:</p> <ul style="list-style-type: none"> • supplied as a 1-pack, 1 ml of a 140 mg/mL solution of evolocumab <p>Repatha SureClick 140 mg/mL single-use prefilled autoinjector:</p> <ul style="list-style-type: none"> • supplied as a 1-pack, 2-pack, and 3-pack, 1 ml of a 140 mg/mL solution of evolocumab

<p>Storage</p>	<p>Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. If removed from the refrigerator, Repatha should be kept at controlled room temperature (up to 25°C [77°F]) in the original carton and must be used within 30 days. Protect Repatha™ from direct light and do not expose to temperatures above 25°C (77°F). Do not freeze. Do not shake.</p>
<p>Container Closure</p>	<p>Repatha Prefilled Syringe:</p> <ul style="list-style-type: none"> • 1 mL Type I glass syringe with a staked-in-place stainless steel needle covered with an (b) (4) needle shield and a (b) (4) (b) (4) plunger-stopper (b) (4). <p>Repatha SureClick Autoinjector:</p> <ul style="list-style-type: none"> • The proposed autoinjector is a modified version of the SureClick autoinjector currently approved for Enbrel (etanercept). • The proposed autoinjector differs from the SureClick autoinjector in: <ul style="list-style-type: none"> — color (b) (4)

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on February 4, 2015 using the term, AMG 145, to identify reviews previously performed by DMEPA. We also searched DARRTS for meeting preliminary comments.

C.2 Results

Our search identified two previous reviews⁸, and we confirmed that our previous recommendations were implemented in the Human Factors Study Protocols.

⁸ Vee S. Human Factors Protocol Comments for AMG 145 (IND 105188). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 Feb 1. 3 p. OSE RCM No.: 2012-2525.

End of Phase 2 Type B Meeting Preliminary Comments (dated 2012 Jul 6).

APPENDIX D. HUMAN FACTORS STUDY

Repatha (Prefilled Syringe)

D.1 Study Design

The Human Factors Study Results and IFU for Repatha submitted on August 27, 2014 were evaluated. Below is a brief overview of the study objectives, description of the study participants, study design, data collection, and data analysis.

Study Objective:

Purpose of this summative study was to validate that the intended user populations could safely and effectively operate the Repatha prefilled syringe, including understanding accompanying Instructions for Use (IFU), to simulate self-administered injection procedures.

Study Participants:

Table 3 provides information on the study participants and demographics.

	N (Female)	Average Age [Range]	BMI >30	Injection Experienced	Injection Naïve	Teaches Injections
Patients	16 (8 F)	63 [33 – 77]	4	4	12	—
Caregivers	15 (9 F)	42 [24 – 68]	—	4	11	—
HCPs	16 (12 F)	—	—	15	1	14
TOTAL	47 (29 F)	—	4	23	24	14

One colorblind HCP was recruited, and he reported his colorblindness did not interfere with his ability to understand the instructions or administer the injection.

Two patients with dexterity issues were recruited for the study:

- One patient reported that her arthritis diagnosis did not interfere with her ability to carry out the tasks.
- Another patient suffered from a stroke and could not use her left arm or hand, requesting assistance from the moderator on some steps of the injection process (patient would likely need assistance from a caregiver).

Training and Testing Sessions:

All participants were self-trained by reading the IFU. Each participant took part in two 60-minute sessions, which were comprised of a pre-interview, reading of the IFU, performing a simulated injection, a set of verbal questions asked to clarify understanding of items that could not be observed, a root cause analysis (where applicable), and debriefing (after completion of the second session). The moderator did not communicate with the participant during task execution. During the testing sessions, if the participant failed to complete a successful injection, the participant was permitted to make a second attempt.

- 1st session: The purpose of the first session was for the participant to self-train how to use the Repatha prefilled syringe using the provided IFU, and then to perform a

simulated injection into a skin pad. The moderator asked participants to read through the IFU and to take as much time as they needed with the instructions to feel comfortable enough to perform an injection on their own. Participants understood instructions could be pulled out of the prefilled syringe carton and referred to during the simulated injection.

- 2nd session: Occurred approximately one week after the initial session to simulate learning or memory decay. Participants were not specifically asked to read the IFU in the second session, but were reminded that the instructions were available in the prefilled syringe carton for them to use.

Participants were provided with a prefilled syringe which was filled with a sterile placebo solution that mimicked the appearance and viscosity of evolocumab and was injected into a skin pad worn by the patient or attached to a mannequin for caregivers and HCPs. Other materials provided included a sharps container for disposal, alcohol wipes, cotton balls, bandages, non-latex gloves, and a non-operational portable sink.

Essential and safety critical steps were assessed through direct observation and targeted questioning (Table 4).

Table 4. Essential and Safety Critical Steps Evaluated		
Steps in AMG 145 PFS IFU	Essential Step	Safety Critical Step
Stores device properly		X
Keeps device out of sight and reach of children to avoid accidental dose by child		X
Retrieves device from storage	X	
Checks that the drug name appears on the carton label (or topweb or primary label)		X
Waits 30 minutes for drug to reach room temperature		
Gathers required supplies		
Washes hands thoroughly		X
Uses clean work surface		X
Selects site	X	
Cleans injection site with an alcohol wipe		X
Removes device from packaging	X	
Checks expiration date		X
Inspects drug appearance		X
Inspect device for damage		X

Removes needle cover without needle stick to avoid infection to during injection	X	X
Disposes needle cover		
Creates a firm skin "platform" into which the needle will pierce the skin.		
Steps in AMG 145 PFS IFU	Essential Step	Safety Critical Step
Places injection needle on injection site surface and pierces the skin	X	
Depresses the syringe plunger rod to inject the drug after piercing skin and maintain pressure on the plunger rod until the stopper bottoms out, to empty the syringe and to deliver a complete dose.	X	
Removes the needle from skin	X	
Disposes of syringe without needle stick to avoid infection to self or third party after injection		X
Examines injection site and apply bandage if necessary		

User Requirements were validated through direct observation and targeted questioning (Table 5).

Table 5. User Needs Requirements			
Feature Number	Feature	Requirement	Acceptance Criteria
UR1	Simple and intuitive injection	Users can self-inject themselves after just reading the IFU. Users can deliver drug product in a minimum number of steps.	User can understand and use the IFU to deliver complete dose.
UR2	Comfortable handling / shape	User can deliver single handed.	User can deliver a complete dose with single handed extrusion.
UR3	Dose delivery status & completion confirmation	Users can have visual indication of status. Users can have tactile and visual confirmation of complete dose delivery while inserted in delivery site.	User can use visual and tactile endpoints to know when dose is completely delivered while needle is inserted in site.
UR4	Self-administration and Caregiver administration	The intended user population can self-administer the injection, or with Caregiver help.	Users can deliver complete dose to self or to the patient

Feature Number	Feature	Requirement	Acceptance Criteria
UR5	Visual Inspection of drug product prior to placement on injection site	Users can judge drug product quality, with no part of the device or the labeling getting in the way of viewing the drug.	User can inspect the drug for quality.
UR6	Avoiding needle stick	Users can use the PFS Combination Product's instructional materials to avoid needle stick before and after injection.	User can handle the combination product without need stick before and after administering an injection.
UR7	Ease of opening packaging and removal of device	The intended user population can use the PFS Combination Product's instructional materials to open the package easily and remove the device safely.	User can remove the device from package safely and effectively.
UR8	Multiple administering positions and angles	Users can achieve a subcutaneous injection while plunging the needle from several positions, depending on the site location Self: abdomen, thigh. Caregiver: back of arm.	User can deliver complete dose into subcutaneous tissue by holding the device at 45-90 degree angle into abdomen, thigh, or back of forearm
UR9	Higher plunging leverage	Users can easily extrude the syringe contents with a direct linear motion.	User can effectively deliver complete dose.
UR10	Identifying the product dose and safety information	Users can read the labeling on the device and packaging when they receive it after shipping and storage.	User can read the product name and expiration on the packaging.
UR11	Reliable experience	Users can extrude syringe contents with a consistent force each time.	User can effectively deliver complete dose.
UR12	Safe and effective drug dose	Users can get a safe effective drug dose.	User Can check drug expiry, inspect drug quality, and successfully deliver a complete dose.

Data Collection and Analysis

Overall injection tasks were categorized as follows:

- Success: participant is able to deliver a complete dose and operate the prefilled syringe without harm to themselves or to others
- Failure: participant is unable to deliver a complete dose or operate the prefilled syringe without harm to themselves or to others

Each individual step in the process of administering an injection was evaluated as a success or failure and any use errors, close calls, and operational difficulties were recorded:

- Use Error: a case in which a user commits an action (or omits an action) that could potentially lead to harm and/or not receiving the prescribed therapy
- Close Call: a case in which a user almost commits a use error, but “catches” him or herself in time to avoid making the use error
- Operational Difficulty: a case in which a user appears to struggle to perform a task

The moderator probed for feedback to determine the root cause of any failures, use errors, operational difficulties, or close calls.

Once root causes for the notable observations were discussed, the moderator moved onto a series of evaluations to assess safety-critical steps that were not possible to determine through direct observation during the injection procedure. Participants were asked:

- to read the product name and expiration date from both the carton and the syringe label to demonstrate legibility
- determine if they could evaluate the syringe contents and the syringe integrity
- additional scenario-based questions assessed the participants’ understanding of proper storage, methods to bring the device to room temperature, clean environment, child safety and single use of the PFS.

The following data was collected:

- Success rate for Essential and Safety Critical Steps
- Success rate for User Requirements
- Success rate for non-essential, non-safety critical steps (those listed in IFU)
- Failures and reported root causes
- Use errors, close calls, operational difficulties, and reported root causes
- Post-task confidence ratings (subjective data) was evaluated on a five-point Likert scale and was obtained to evaluate:
 - participants’ perception of the difficulty in understanding the IFU,
 - confidence they could perform an injection, and
 - perceived level of difficulty administering the injections.

Participants completed five-point Likert scales, and the moderator probed participants who rated the instructions or the injection process as “very difficult”, “difficult” or “neither difficult nor easy” (ratings of 3 or less) for greater understanding.

- Participant feedback: at the end of the session, participants were encouraged to offer feedback on anything that could be clarified in the IFU, or anything that could improve the ease of following the instructions and administering an injection

The moderator noted differences in performance from the 1st session, including decay of learning effects in the 2nd session.

Study Limitations (per the Sponsor)

- Participants reported feeling more resistance than expected when giving the injection, and this could be the result of injecting into a skin pad, rather than into real skin.
- Research facility did not have a working sink in the test room, but a portable nonoperational sink was brought into the room so participants could simulate washing hands.
- Participants were provided with cartons at room temperature after they were retrieved from the refrigerator.

D.2 Results

Table 6. Results of Essential and Safety Critical Steps – Repatha Prefilled Syringe									
Steps* <small>* E=Essential; SC=Safety Critical</small>	Failures Observed in Session 1				Failures Observed in Session 2				Session 1 and 2 Total Failures
	Patients (n=16)	Caregivers (n=15)	HCPs (n=16)	Session 1 Total Failures	Patients (n=16)	Caregivers (n=15)	HCPs (n=16)	Session 2 Total Failures	
Stores device properly in the refrigerator (SC)	0	2	0	2	0	0	0	0	2
Keeps device out of sight and reach of children to avoid accidental dose by child (SC)	0	0	0	0	0	0	0	0	0
Retrieves device from storage (E)	0	0	0	0	0	0	0	0	0
Checks that the drug name appears on the carton label (or topweb or primary label) (SC)	0	0	0	0	0	0	0	0	0
Wait 30 minutes for drug to reach room temperature	3	1	3	7	1	1	1	3	10
Washes hands thoroughly (SC)	7	2	0	9	1	1	0	2	11
Gathers required supplies	0	0	0	0	0	0	0	0	0
Uses clean work surface (SC)	0	0	0	0	0	0	0	0	0
Selects injection site (E)	0	0	0	0	0	0	0	0	0

Steps* * E=Essential; SC=Safety Critical	Failures Observed in Session 1				Failures Observed in Session 2				Session 1 and 2 Total Failures
	Patients (n=16)	Caregivers (n=15)	HCPs (n=16)	Session 1 Total Failures	Patients (n=16)	Caregivers (n=15)	HCPs (n=16)	Session 2 Total Failures	
Cleans injection site with alcohol wipe (SC)	2	1	3	6	0	1	1	2	8
Removes device from packaging (E)**	0	0	0	0**	0	0	0	0**	0
Checks expiration date (SC)	7	7	4	18	0	2	1	3	21
Inspects drug appearance (SC)	4	3	2	9	0	1	0	1	10
Inspect device for damage (SC)	3	2	0	5	0	1	0	1	6
Removes needle cover without needle stick to avoid infection during injection (E, SC)	0	0	0	0	0	0	0	0	0
Disposes needle cover	0	0	0	0	0	0	0	0	0
Creates a firm skin “platform” into which the needle will pierce the skin	2	2	0	4	2	1	0	3	7
Places injection needle on injection site surface and pierces the skin (E)	0	0	0	0	0	0	0	0	0

**Although participants were able to remove the device from the packaging, 72% (34/47) of the participants in Week 1 and 64% (30/47) of the participants in Week 2 reported operational difficulty in opening the outer carton.

Steps* * E=Essential; SC=Safety Critical	Failures Observed in Session 1				Failures Observed in Session 2				Session 1 and 2 Total Failures
	Patients (n=16)	Caregivers (n=15)	HCPs (n=16)	Session 1 Total Failures	Patients (n=16)	Caregivers (n=15)	HCPs (n=16)	Session 2 Total Failures	
Depresses the plunger rod to inject the drug after piercing skin and maintain pressure on the plunger rod until the stopper bottoms out, to empty the syringe and deliver a complete dose (E)	1	1	0	2	2	1	0	3	5
Removes the needle from skin (E)	0	0	0	0	0	0	0	0	0
Disposes of syringe without needle stick to avoid injection to self or third party after injection (SC)	0	0	0	0	0	0	0	0	0
Examines injection site and apply bandage if necessary	0	0	0	0	1	0	0	1	1
Total Failures	29	21	12	62	7	9	3	19	81

Overview:

- 96% (45/47) of the participants in the first week, and 94% (44/47) of the participants in the second week successfully injected a complete dose of placebo into the skin pad with the PFS.
- In both sessions, 2 participants failed to complete the injection on the first attempt. 1 participant who performed a successful injection in the first session, failed to complete the injection in the second session, also on the first attempt only.

Detailed Results:

Table 7. Essential and Safety Critical Steps with Results				
Steps for AMG 145 PFS	E	SC	HFE Summative Results	Root Cause and Further Clarification
Stores device properly		X	In week 1, 100% of the HCPs, 87% (13/15) of the caregivers, and 100% of the patients said the device should be stored in the refrigerator. In week 2, 100% of the participants correctly stated that the device should be stored in the refrigerator.	One caregiver said the device should be stored in a cool dry place, and the other caregiver said he wasn't sure, and suggested a cupboard. The two caregivers who failed to say the device should be stored in the refrigerator said they did not see this information in the IFU (perceptual failure).
Keeps device out of sight and reach of children to avoid accidental dose by child		X	100% of the participants said the device should be kept out of sight and reach of children in both sessions.	
Retrieves device from storage	X		100% of the participants successfully retrieved the device from storage in both sessions.	
Checks that the drug name appears on the carton label (or topweb or primary label)		X	100% of the participants successfully checked the drug name on the carton label.	

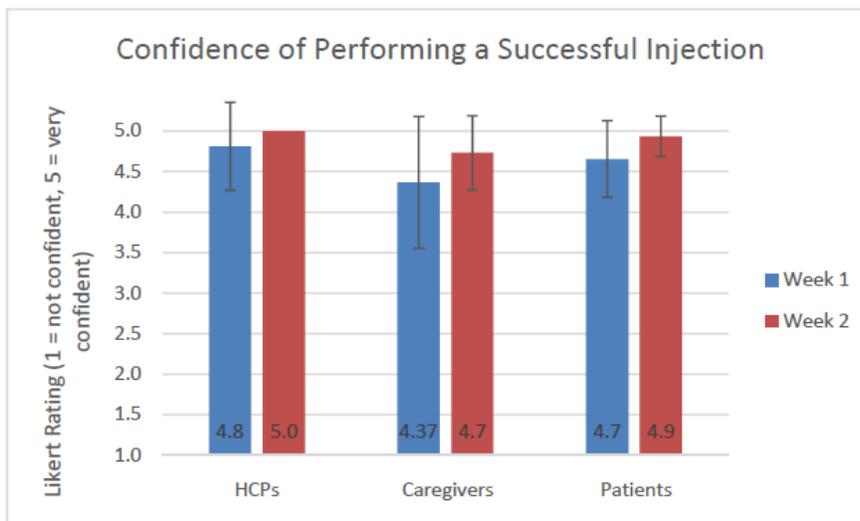
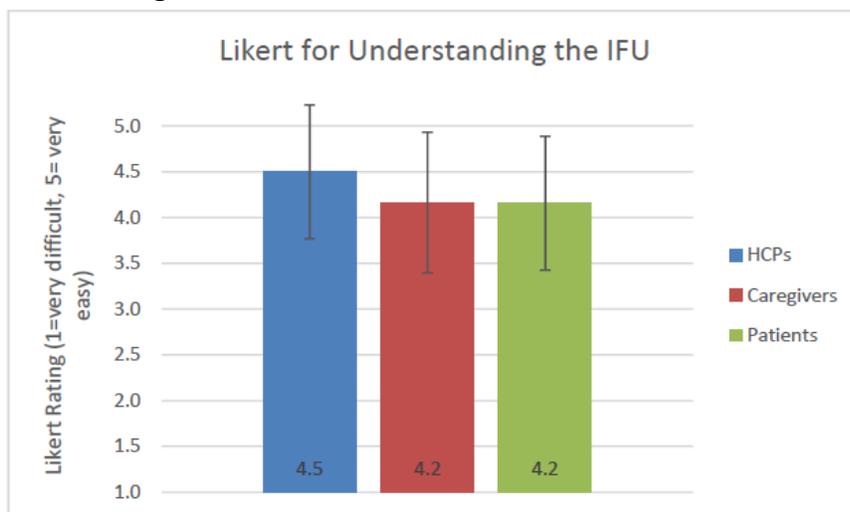
Steps for AMG 145 PFS	E	SC	HFE Summative Results	Root Cause and Further Clarification
Wait 30 minutes for drug to reach room temperature			<p>In week 1, 81% (13/16) of the HCPs, 93% (14/15) of the caregivers, and 81% (13/16) of the patients said they would wait for the device to reach room temperature.</p> <p>In week 2, 94% (15/16) of the HCPs, 93% (14/15) of the caregivers, and 94% (15/16) of the patients said they would wait for the device to reach room temperature.</p>	<p>Across both weeks, of the participants who failed to say they would wait 30 minutes:</p> <p>-Five participants said they did not see this information in the IFU (perceptual failure).</p> <p>-Five participants said they remembered reading the information, but they forgot to mention they would wait while giving the injection (cognitive failure).</p>
Washes hands thoroughly		X	<p>In week 1, 100% of the HCPs, 87% (13/15) of the caregivers, and 56% (9/16) of the patients washed their hands.</p> <p>In week 2, 100% of the HCPs, 93% (14/15) of the caregivers, and 94% (15/16) of the patients washed their hands.</p>	<p>Across both weeks, of the participants who failed to wash their hands:</p> <p>-All of the 11 cases of failure can be attributed to the study environment.</p>
Gathers required supplies			100% of the participants successfully gathered supplies in both sessions.	
Uses clean work surface		X	100% of the participants understood that a clean work surface was required.	
Selects site	X		100% of the participants successfully selected a valid injection location in both sessions.	
Cleans injection site with an alcohol wipe		X	<p>In week 1, 81% (13/16) of the HCPs, 93% (14/15) of the caregivers, and 88% (14/16) of the patients cleaned the injection site.</p> <p>In week 2, 94% (15/16) of the HCPs, 93% (14/15) of the caregivers, and 100% patients cleaned the injection site.</p>	<p>Across both weeks, of the participants who failed to clean the injection site:</p> <p>-All of the 8 cases of failure to clean the injection site can be attributed to the study environment.</p>
Removes device from packaging	X		100% of the participants successfully removed the device from the packaging without assistance.	<p>Although participants were able to remove the device from packaging, in week 1, 72% (34/47) of the participants reported an operational difficulty opening the outer carton.</p> <p>In week 2, 64% (30/47) of the participants reported an operational difficulty opening the outer carton.</p>

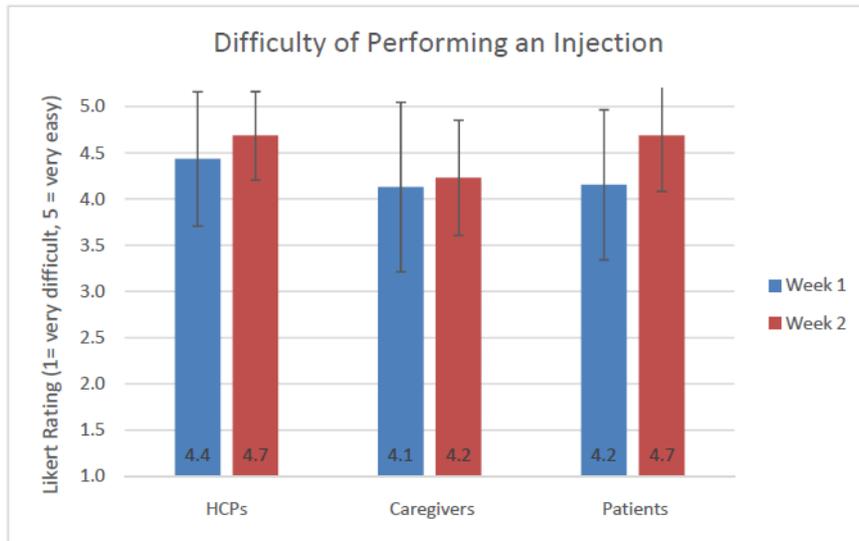
Steps for AMG 145 PFS	E	SC	HFE Summative Results	Root Cause and Further Clarification
Checks expiration date		X	In week 1, 75% (12/16) of the HCPs, 53% (8/15) of the caregivers, and 56% (9/16) of the patients checked the expiration date. In week 2, 94% (15/16) of the HCPs, 87% (13/15) of the caregivers, and 100% of the patients checked the expiration date.	Across both weeks, all of the participants who did not check the expiration date said they did not see this step in the IFU (perceptual failure).
Inspects drug appearance		X	In week 1, 88% (14/16) of the HCPs, 80% (12/15) of the caregivers, and 75% (12/16) of the patients inspected the drug appearance. In week 2, 100% of the HCPs, 93% (14/15) of the caregivers, and 100% of the patients inspected the drug appearance.	Across both weeks, of the participants who failed to inspect drug appearance: -For all of the 10 cases of failure, participants said they did not see this step on the IFU (perceptual failure).
Inspect device for damage		X	In week 1, 100% of the HCPs, 87% (13/15) of the caregivers, and 81% (13/16) of the patients inspected the syringe for damage. In week 2, 100% of the HCPs, 93% (14/15) of the caregivers, and 100% of the patients inspected the syringe for damage.	Across both weeks, of the participants who failed to inspect the device for damage: -For all 6 of the cases of failure, participants said they did not see this step on the IFU (perceptual failure).
Removes needle cover without needle stick to avoid infection to during injection	X	X	100% of the participants removed the needle cover without difficulty in both sessions. Needle stick was avoided for all participants.	
Disposes needle cover			100% of the participants successfully disposed the needle cover in both sessions.	

Steps for AMG 145 PFS	E	SC	HFE Summative Results	Root Cause and Further Clarification
Creates a firm skin "platform" into which the needle will pierce the skin.			<p>In week 1, 100% of the HCPs, 87% (13/15) of the caregivers, and 88% (14/16) of the patients pinched the skin pad.</p> <p>In week 2, 100% of the HCPs, 93% (14/15) of the caregivers, and 88% (14/16) of the patients pinched the skin pad.</p>	<p>Across both weeks, of the participants who failed to pinch the skin pad:</p> <ul style="list-style-type: none"> -Three participants said they remembered reading this instruction, but forgot in the moment (cognitive failure). - One participant had the use of only one hand and was unable to pinch the skin pad. -One participant said she did not think the skin pad could be pinched, which is a study artifact. -One participant believed pinching was only necessary if injecting into the belly, as is shown in the IFU.
Places injection needle on injection site surface and pierces the skin	X		100% of the participants successfully pierced the injection site in both sessions.	
Depresses the syringe plunger rod to inject the drug after piercing skin and maintain pressure on the plunger rod until the stopper bottoms out, to empty the syringe and to deliver a complete dose.	X		<p>In week 1, 100% of the HCPs, 94%, (15/16) of the patients, and 93% (14/15) of the caregivers successfully delivered a complete dose.</p> <p>In week 2, 100% of the HCPs, 93% (14/15) of the caregivers, and 88% (14/16) of the patients successfully delivered a complete dose.</p>	<p>Across both weeks, of the participants who failed to depress the plunger rod until the stopper bottoms out:</p> <ul style="list-style-type: none"> -One of the cases of failure (patient, week 2) can be attributed to the participant's inaccurate perception that the injection had completed. She removed the syringe prematurely, explaining she felt resistance on the syringe, which led her to believe the injection was complete. -The other four cases of failure can be attributed to study artifacts <p>See the "Failure to Inject" section for more detailed information.</p>
Removes the needle from skin	X		100% of the participants successfully removed the needle from the skin pad in both sessions.	
Disposes of syringe without needle stick to avoid infection to self or third party after injection		X	100% of the participants disposed the syringe without needle stick in both sessions. 100% of the participants successfully disposed the used syringe in the sharps container.	

Steps for AMG 145 PFS	E	SC	HFE Summative Results	Root Cause and Further Clarification
Examine injection site and apply bandage if necessary			<p>In week 1, 100% of the HCPs, 100% of the caregivers, and 100% of the patients examined the injection site after completing the injection.</p> <p>In week 2, 100% of the HCPs, 100% of the caregivers, and 94% (15/16) of the patients examined the site after completing the injection.</p>	The one case of failure to examine the injection site can be attributed to the artificial study environment.

Likert Ratings:





Repatha SureClick (Prefilled Pen/Autoinjector)

D.3 Study Design

The Human Factors Study Results and IFU for Repatha SureClick submitted on August 27, 2014 were evaluated. Below is a brief overview of the study objectives, description of the study participants, study design, data collection, and data analysis.

Study Objectives:

- Primary objective: to validate that the Repatha SureClick Autoinjector is safe and effective for use.
- Secondary objectives:
 - Validate that participants with minimal training can safely and effectively use the autoinjector
 - Validate that participants avoid needle pricks during any of the injection steps

Study Participants:

Table 8 provides information on the study participants and demographics.

Table 8. Distinct End User Groups			
User Groups	Trained (Return session)	Untrained (Single session)	Total
Patients Age ranged from 34 to 78 years old. No participants had severe hand dysfunction, but some had additional co-morbidities including arthritis, hypertension, and diabetes. 88% of patients reported vision impairment.	10 injection experienced*	6 injection experienced*	16
	9 injection naïve	9 injection naïve	18
Total	19**	15	34
Caregivers Supported patients with medication support and 100% of participants currently cared for patients diagnosed with high cholesterol.	10 injection experienced	11 injection experienced	21
	5 injection naïve	5 injection naïve	10
Total	15	16	31
HCPs nurses from general/ internal medicine practice, endocrinology practice, or cardiology practice	17 injection experienced***	14 injection experienced**	31
	1 injection naïve	1 injection naïve	2
Total	18	15	33
Total	52	46	98

*Injection experienced defined as experience in self-injecting and experience injecting others

** Although 19 “trained patients” participated in the first session, 18 participants returned for the second session

***Currently teaches patients to self-inject

Training and Testing Sessions:

Half of the participants (n=52) received rudimentary training and attended two 60-minute one-on-one usability test sessions, approximately 1 week apart

- Moderator walked the participant through the process required to properly use the device, using the IFU as a visual aid (i.e., the moderator narrated the injection process and pointed to the appropriate steps in the IFU so that the participant could follow along and see an illustration of the instructions).
- Participants were then given time to review the IFU, if they chose to, and had an opportunity to ask questions.
- Participants were asked to leave the room and wait in the lobby for 15 minutes before performing the simulated injection. The 15-minute delay was meant to simulate the

action of users leaving the doctor's office, picking up their medication, and heading home.

- To assess learning decay, trained participants returned for a second session approximately one week later and were asked to perform another simulated injection without any additional training.

The other half of the participants (n=46) received no formal training and attended a single 60-minute one-on-one usability test session.

- Participants in the untrained group were provided with the kit they would receive from the physician or pharmacist. All materials were available to them (i.e., IFU, RG) and could use whatever materials they wanted to help them with the injection.
- Participants were not forced to read the instructions prior to performing the injection as they may or may not read the instructions in the real world.

Patients were asked to perform a simulated injection on themselves using an injection pad, while caregivers and HCPs were asked to perform a simulated injection on a patient (represented by a mannequin) using an injection pad.

- Materials: Participants were provided with two AMG 145 AI/pen devices, Instructions for Use (IFU), Reference Guide (RG), and a Physicians Insert and were able to use any available material to help them with the injection.
- Moderator did not offer suggestions or provide verbal comments during task execution and did not intervene at any point while participants attempted tasks unless it was necessary (in the event that the participant initiated potentially hazardous actions).

The device was validated against the essential and critical (high risk) tasks:

- Essential tasks: tasks/steps that are necessary for the proper operation of the device
- Critical tasks: tasks/steps that are most likely to be associated with use error that could cause clinical harm to the patient or other use.
- Other tasks were evaluated as part of the overall injection workflow and did not have an impact on the overall success of an injection attempt.
- For an overall injection attempt to be successful, there must not have been any failures on any of the essential or critical tasks.

Essential and safety critical steps were assessed through direct observation and targeted questioning (Table 9).

Table 9. Essential and Critical Tasks Evaluated

#	Task	Critical or Essential	User	User Needs Requirement	Study Technique	Success Criteria
1	Remove AI device from package	Essential	Patients Caregivers HCPs	UR1 UR 2	Participants were observed if they could remove the AI device from packaging.	Must remove AI from package without damaging the AI device.
2	Choose the injection site	Essential	Patients Caregivers HCPs	UR17	Participants were observed whether they chose to inject into one of the approved injection sites.	Must perform injection into the thigh or abdomen (for HCPs and Caregiver groups, the arm is also acceptable).
3	Remove orange cap	Essential	Patients Caregivers HCPs	UR1 UR 2	Participants were observed if they could remove the orange cap.	Participants must remove the orange cap prior to performing the injection.
4	Activate AI by pushing down firmly on injection site and pressing grey button	Essential	Patients Caregivers HCPs	UR1 UR 2 UR13	Participants were observed whether they firmly pushed the AI down on the injection site and pressed the grey button to activate the device.	Participants must press down hard enough to unlock the AI and press the grey button to activate the AI.
5	Continue to hold AI against skin until injection is complete	Essential	Patients Caregivers HCPs	UR1 UR 2 UR5 UR11	Participants were observed whether they continued to hold the AI against the skin until the injection was complete.	Participants must continue to hold the AI against the skin until the injection is complete. They know the injection is complete either by (1) seeing the medication window turn yellow, (2) waiting 15 seconds, and/or (3) hearing a click.

The study also validated additional user need requirements (See Table 10).

Table 10. Additional Tasks Evaluated					
#	User	UNR #	User Needs Requirement	Study Technique	Success Criteria
1	Patients Caregivers	UR8	The Autoinjector and related Instructional material must be designed for self-administration and caregiver administration by users with minimal education	Participants were asked a question about ease of use of the IFU and RG.	Participant must answer that the instructions for use are easy to understand and provided all the required information for use of the AI
2	Patients Caregivers HCPs	UR3	Feature to prevent accidental needle stick injury	Participants were observed through their handling of the AI for any needle stick.	Participant must not get a needle stick during their handling of the device until disposal.

Data Collection and Analysis

Task was considered complete when the participant indicated that they had completed the injection.

- Following each simulated injection, whether successful or not, participants provided feedback on their experience pertaining to their confidence that they performed a successful simulated injection.
- If the participant indicated that they had not completed the injection and would inject using a second autoinjector, the moderator did not interfere and allowed the participant to proceed as they would if they were alone at home or in the office.

If a participant failed in any of the essential steps in the injection process, the overall injection was considered a failure.

- If a participant failed the first injection attempt, the moderator asked the participant to imagine it was a week later and asked the participant to administer that second injection.
- The moderator probed to uncover the root cause of the failure and/or close call. For the trained group, any failures during the first visit were followed up with probing to understand the root cause of those failures during the first visit.
- Participants who did not push the device firmly enough against the injection site to trigger the device were given an additional device during root cause probing and walked through the injection process by the moderator so that they were able to perform steps they had not yet performed and therefore, to more fully understand and recount the root cause of any failure.

The following data was collected:

- Success rate for critical and/or essential steps
 - Participant independently accomplished the critical and/or essential steps in the injection process, regardless of the duration it took to complete the step or support materials used to complete the injection.
- Failures/use errors and reported root causes
 - Failure to complete any of the critical and/or essential steps in the injection process.
 - Participant stated they were done with the task without having successfully completed an injection.
 - Participant requested to call their physician or customer support for help with a safety-critical or essential task.
 - Participant stated that they want/need to give up and do not attempt any further assistance from support materials.
- Close calls (observed and participant self-reported) and reported root causes
 - Any instance of a potential failure that could have led to harm that was avoided by vigilance on the part of the user.
- Instances of guidance: moderator provided assistance in cases where the participant indicated that they cannot complete the task and would contact their physician or customer support for help.
- Foreseeable misuse: Any instance of a purposeful ignoring of safety measures detailed in the IFU or RG.

Limitations (per the Sponsor)

- For the trained group, any failures during the first visit were followed up with probing to understand root cause of those failures during the first visit. This may affect/bias the participants' performance in the second visit.
- Unplugged refrigerator in the testing environment led some participants to not mention that they would wait 30 minutes for the device to come to room temperature (because the device was already at room temperature).

D.4 Results

Overview:

69.4% (68/98) participants successfully administered an injection on their first or only visit (note: trained participants came in for two visits).

- Of the trained participants who returned for a second session 1 week later, 90.2% (46/51) participants successfully administered an injection.

Table 11. Successes Observed on Each Essential Step During First and/or Only Visit				
Step	Task	Essential or Critical	Success Criteria	# of Successes Observed/# of Attempts
1	Remove AI device from package	Essential	Must remove AI from package without damaging AI device	98/98 (100%)
2	Choose the injection site	Essential	Must perform injection into the thigh or abdomen (for HCPs and caregivers, the arm is also acceptable)	91/98 (92.9%)
3	Remove the orange cap	Essential	Must remove the orange cap prior to performing the injection	97/98 (99%)
4	Activate AI by pushing down firmly on injection site and pressing grey button	Essential	Participants must press down hard enough to unlock the AI and press the grey button to activate the AI	81/97 (83.5%)
5	Continue to hold AI against skin until injection is complete	Essential	Participants must continue to hold the AI against the skin until the injection is complete. They know the injection is complete either by (1) seeing the medication window turn yellow, (2) waiting 15 seconds, and/or (3) hearing a click	73/82 (89%)*

Note: failures in Steps 3 or 4 below prevented the participant from attempting the subsequent steps, therefore decreasing the overall number of participants who attempted these steps.

*One participant attempted to inject upside down and was told by the moderator to turn the AI. He went on to perform Step 5, explaining why the total number of participants who attempted Step 5 is one higher than the number of participants who did not activate the AI (Step 4).

Table 10. Failures Observed on Essential Steps During First and Second Visits – Repatha SureClick Autoinjector								
Task	Session #	Trained (Attended 2 sessions)			Untrained (Attended 1 session)			Total Errors
		Patients	Caregivers	HCPs	Patients	Caregivers	HCPs	
Remove AI device from package	Session 1	0	0	0	0	0	0	0
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		0	0	0	0	0	0	0
Choose the injection site	Session 1	1 (1 injection experienced)	0	0	3 (2 injection naïve, 1 injection experienced)	3 (3 injection experienced)	0	7
	Session 2	0	0	0	N/A	N/A	N/A	0
Total Errors – Sessions 1 & 2		1	0	0	3	3	0	7
Remove the orange cap	Session 1	0	0	0	1 (1 injection naïve)	0	0	1
	Session 2	0	1 (1 injection experienced)	0	N/A	N/A	N/A	1
Total Errors – Sessions 1 & 2		0	1	0	1	0	0	2
Activate AI by pushing down firmly on injection site and pressing grey button	Session 1	1 (1 injection naïve)	1 (1 injection experienced)	3 (3 injection experienced)	3 (2 injection naïve, 1 injection experienced)	3 (1 injection naïve, 2 injection experienced)	5 (5 injection experienced)	16
	Session 2	0	2 (2 injection experienced)	2 (2 injection experienced)	N/A	N/A	N/A	4
Total Errors – Sessions 1 & 2		1	3	5	3	3	5	20

Task	Session #	Trained (Attended 2 sessions)			Untrained (Attended 1 session)			Total Errors
		Patients	Caregivers	HCPs	Patients	Caregivers	HCPs	
Continue to hold AI against skin until injection is complete	Session 1	2 (2 injection naïve)	0	1 (1 injection experienced)	2 (1 injection naïve, 1 injection experienced)	2 (2 injection naïve)	2 (2 injection experienced)	9
	Session 2	0	0	1 (1 injection experienced)	N/A	N/A	N/A	1
Total Errors – Sessions 1 & 2		2	0	2	2	2	2	10
Total Errors – All Tasks		4	4	7	9	8	7	39

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/s/

MISHALE P MISTRY
04/13/2015

YELENA L MASLOV
04/15/2015



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: January 16, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Kati Johnson, RPM
DMEP

Subject: QT-IRT Consult to BLA 125522

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 9/8/2014 regarding the sponsor's Integrated Cardiac Safety Report and proposed labeling. The QT-IRT received and reviewed the following materials:

- Your consult
- Integrated Cardiac Safety Report
- Proposed labeling
- QT-IRT's QT waiver review (7/2/2012 under IND 105188)

QT-IRT Comments for DMEP

Evolocumab as a large targeted protein has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical data to suggest that evolocumab has the potential to delay ventricular repolarization. The proposed labeling by the sponsor is reasonable.

Thank you for requesting our input into the development of this product under BLA 125522. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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

/s/

JIANG LIU
01/16/2015

NORMAN L STOCKBRIDGE
01/16/2015

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# 125522	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Repatha/Repatha SureClick Established/Proper Name: Evolocumab Dosage Form: solution for injection Strengths: 140 mg/mL		
Applicant: Amgen Corp. Agent for Applicant (if applicable): N/A		
Date of Application: 8/27/2014 Date of Receipt: 8/27/2014 Date clock started after UN: N/A		
PDUFA Goal Date: 8/27/2015		Action Goal Date (if different): N/A
Filing Date: 10/25/2014		Date of Filing Meeting: 10/8/2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indications: treatment of primary dyslipidemia and mixed dyslipidemia and homozygous familial hypercholesterolemia (HoFH)		
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): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>		
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 checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? N/A		Resubmission after refuse to file? N/A
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 checked="" 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	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Other (drug/device/biological product)

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation (for 1 indication) <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <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 (if OTC product): N/A				
List referenced IND Number(s): 105188				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <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 tracking system.</i>	X	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, 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>	X	<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"/>	X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ 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) included with authorized signature?	X	<input type="checkbox"/>		

<u>User Fee Status</u>		Payment for this application:		
<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. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		<input checked="" type="checkbox"/> Paid <input 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. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears		
505(b)(2)	YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)				
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"/>	<input type="checkbox"/>	
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"/>	<input type="checkbox"/>	
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)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If you answered yes to any of the above 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</i>				
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, please list below:				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, 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 will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan	<input type="checkbox"/>	<input type="checkbox"/>		

<p>exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>				
<p>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)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>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)?</p> <p><i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i></p> <p><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></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Format and Content	
<p>Do not check mixed submission if the only electronic component is the content of labeling (COL).</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</p>	

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>	X	<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>	X	<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>	X	<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"/>	X	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	X	

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, 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>	X	<input type="checkbox"/>		
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
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>	X	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	X	<input type="checkbox"/>	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <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>	X	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	X	<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 type="checkbox"/>	<input type="checkbox"/>	X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X	<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?	<input type="checkbox"/>	<input type="checkbox"/>		

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) 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)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 10/8/2014

BLA #: 125522

PROPRIETARY NAME: Repatha

ESTABLISHED/PROPER NAME: Evolocumab

DOSAGE FORM/STRENGTH: 140 mg/mL injection solution

APPLICANT: Amgen Corp

PROPOSED INDICATIONS: Repatha (evolocumab) is a PCSK9 inhibitor indicated as an adjunct therapy to diet to:

Reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with hyperlipidemia or mixed dyslipidemia.

- in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
- alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia.

BACKGROUND: IND 105188 was initially submitted May 14, 2009. Evolocumab (also referred to as AMG 145) is a fully human monoclonal immunoglobulin G2 that specifically binds to proprotein convertase subtilisin/kexin type 9 (PCSK9) and inhibits the interaction between PCSK9 and the low-density lipoprotein receptor (LDLR). This leads to increased LDLR cell surface expression and subsequent decreased circulating concentrations of LDL-C.

The proposed indications for the initial BLA are listed above.

The firm is proposing to market the following presentations:

1. Prefilled syringe (PFS) (140 mg/mL). For this presentation, the drug product is supplied as a sterile, single-use, preservative-free solution for subcutaneous (SC) injection, and contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab.
2. Prefilled autoinjector/pen (AI/pen) (140 mg/mL). This is a single-use, disposable, handheld mechanical injection device that administers, over a 15 second period, a fixed dose of evolocumab into SC tissue.

The proposed dosing regimens for the Hyperlipidemia/Mixed Dyslipidemia indications are 140 mg evolocumab administered SC every 2 weeks (Q2W) or 420 mg administered SC once monthly. The proposed dosing regimen for the HoFH indication is 420 mg SC once monthly or Q2W.

Both the PFS and the AI are appropriate for SC administration every 2 weeks (Q2W). For the 420 mg dose option, patients will currently use 3 AI pen devices per dose. (b) (4)

[REDACTED]

[REDACTED] (b) (4)

A Special Protocol Assessment (SPA) review was requested for the following protocols:

1. Study 114976, entitled *104-Week Subcutaneous Lifetime Pharmacology Study in Hamsters*. The protocol was submitted August 11, 2011, and an agreement letter was issued September 1, 2011.
2. A cardiovascular outcomes trial (CVOT)(Protocol 20110118) entitled *A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Assessing The Impact Of Additional LDL Cholesterol Reduction On Major Cardiovascular Events When AMG 145 is Used In Combination With Statin Therapy In Patients With Clinically Evident Cardiovascular Disease* (FOURIER). The protocol was submitted on October 1, 2012, and an agreement letter was issued January 31, 2013. The protocol was modified in a submission dated October 23, 2013; the revisions were found acceptable and the firm was notified in a letter dated November 21, 2013.

An End-of-Phase 2 (EOP2) clinical meeting was held on July 10, 2012.

An EOP2 meeting to discuss chemistry, manufacturing and controls (CMC) topics was held on November 2, 2012.

A Pre-BLA (CMC only) meeting was held on January 24, 2014.

A Pre-BLA clinical meeting was held on April 10, 2014.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kati Johnson	Y
	CPMS/TL:	Pam Lucarelli	N
Cross-Discipline Team Leader (CDTL)	Jim Smith		Y
Clinical	Reviewer:	Eileen Craig	Y
	TL:	Jim Smith	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:	N/A	

Clinical Pharmacology	Reviewer:	Sury Sista/Justin Earp	Y/N
	TL:	Immo Zadezensky/Ninta Mehrotra	Y/N
Biostatistics	Reviewer:	Susie Sinks	Y
	TL:	Mark Rothmann	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Lee Elmore	Y
	TL:	Karen Davis Bruno	N
Statistics (carcinogenicity)	Reviewer:	Atiar Rahman	N
	TL:	Karl Lin	N
Immunogenicity (assay/assay validation) <i>(for BLAs/BLA efficacy supplements)</i>	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Sang Bong Lee/Bazaraa Damdinsuren	Y/Y
	TL:	Chana Fuchs	Y
Microbiology (sterility)	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	Sang Bong Lee/Bazaraa Damdinsuren	Y/Y
	TL:	Chana Fuchs	Y
Facility Review/Inspection	Reviewer:	Mike Shanks/Lakshmi Narasimhan	Y/Y
	TL:	Patricia Hughes	Y
OSE/DMEPA (proprietary name)	Reviewer:	Mishale Mistry	N
	TL:	Yelena Maslov	N
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	Y
	TL:	Doris Auth	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Lana Shiu-CDRH Selena Ready/Chris Jones-OSE/DPV Robin Duer-Patient Labeling		
Other attendees	Sara Stradley-ODE II Abimbola Adebawale-DMEP Assoc. Director for Labeling (Acting)		

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., BA/BE studies):</p>	<p>X Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<p>X YES</p> <p><input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<p>X Not Applicable</p>
<p>CLINICAL</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p>X FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p>X Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? 	<p>X YES</p> <p><input type="checkbox"/> NO</p>

<p>If no, explain:</p>	
<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> 	<p>X YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined</p> <p>Reason:</p>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<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>	<p>X Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<p>X Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<p><input type="checkbox"/> YES X NO</p>
<p>BIostatistics</p>	<p><input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE</p>

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable X FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	X Not Applicable <input 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 X FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	X YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	X Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input 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</u></p> <p>Comments: N/A</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 type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>none</p>
<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	
<p>Signatory Authority: Curt Rosebraugh, MD/Mary Parks, MD</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 1/29/2015</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
X	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p>X Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<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 type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>
<input type="checkbox"/>	<p>Conduct a PLR format labeling review and include labeling issues in the 74-day letter</p>
<input type="checkbox"/>	<p>Update the PDUFA V DARRTS page (for NME NDAs in the Program)</p>
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	<p>Other</p>

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

/s/

KATI JOHNSON
11/24/2014

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

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

Application: BLA 125522

Application Type: New BLA

Name of Drug/Dosage Form: Repatha (evolocumab) injection-prefilled syringe
Repatha SureClick (evolocumab)-autoinjector

Applicant: Amgen Inc.

Receipt Date: August 27, 2014

Goal Date: August 27, 2015

1. Regulatory History and Applicant's Main Proposals

Repatha (evolocumab) is a PCSK9 inhibitor indicated as an adjunct therapy to diet to:

Reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and to increase HDL-C and ApoA1 in adults with hyperlipidemia or mixed dyslipidemia.

- in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
- alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

Reduce LDL-C, TC, ApoB and non-HDL-C, in patients at least 12 years of age with homozygous familial hypercholesterolemia.

The applicant is proposing to market a prefilled syringe and an autoinjector for bi-weekly or monthly administration.

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 for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

Minor SRPI format deficiencies were identified in the review of this PI. The sponsor was notified and will be corrected in the revised labeling to be submitted the week of November 24, 2014, which will include the agreed-upon tradename Repatha (prefilled syringe) and Repatha SureClick (autoinjector).

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-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 A for a sample tool illustrating the format for the Highlights.

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: *If the length of the columns are balanced, then the HL will conform to the one-half page requirement*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

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 A for a sample tool illustrating white space in HL.

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. Section headings must be presented in the following order in HL:

Section	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 the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

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 in HL 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 heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading 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 should be centered immediately beneath the heading and appear in *italics*.

Comment:

- NO** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading 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 the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in 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) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. 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) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. 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** 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

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *Firm will be requested to right justify this date*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. 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** 27. The same heading 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** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. 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 (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of 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** 32. 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 Labor and Delivery
8.3 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** 33. 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)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- NO** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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: *In the verbatim statement above, firm has used "studies" instead of "trials".*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), 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:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) 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 A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]

Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)]

[m/year]

[section (X.X)]

[m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 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

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 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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/s/

KATI JOHNSON
11/24/2014

**Determining When Pre-License / Pre-Approval Inspections are Necessary
Inspection Waiver Memorandum**

Date: November 24, 2013

From: Lakshmi Rani Narasimhan, Ph.D., OC/OMPQ/DGMP/BMAB
Sang Bong Lee, Ph.D., OPS/OBP/DMA

To: BLA File, STN 125522/0

Through: Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/OMPQ/DGMP/BMAB

Subject: Recommendation to waive a pre-license inspection

Applicant: Amgen Inc.

Facility: Amgen Manufacturing Ltd (AML), Road 31, Kilometer 24.6, Juncos,
Puerto Rico 00777 USA (FEI # 1000110364) - Pre-filled syringe (PFS)
and Autoinjector (AI)/Pen

Product: Evolocumab (Repatha)

Dosage: Sterile, preservative-free liquid formulation in a single-use PFS or AI/Pen
for subcutaneous injection with a dose of 140mg/mL delivered in 1.0 mL.

Indication: For the treatment of primary hyperlipidemia or mixed dyslipidemia in
adults and for homozygous familial hypercholesterolemia (HoFH) in
adults and adolescents aged 12 years and above.

Waiver Recommendation

We recommend that the pre-approval inspection of the Amgen Manufacturing Ltd (AML), Puerto Rico (FEI# 1000110364) which manufactures the Evolocumab Pre-filled syringe) and Autoinjector (AI)/Pen be waived. AML was inspected by BMAB with the district on March 24 - 28, 2014 and the inspection was VAI. The SVS and TRP profiles are acceptable from a CGMP perspective.

Summary

Amgen Inc. submitted a new biologics license application, STN 125522 to license Evolocumab for the treatment of hyperlipidemia or mixed dyslipidemia in adults and homozygous familial hypercholesterolemia (HoFH) in adults and in adolescents aged 12 years and above. Evolocumab is a human monoclonal antibody produced in Chinese

hamster ovary (CHO) cells. Drug substance is manufactured by (b) (4)
(b) (4) The drug product is supplied as a sterile, preservative-free solution containing 140 mg/mL evolocumab in 220 mM proline, 20 mM acetate, 0.01% (w/v) polysorbate 80, pH 5.0 in 1.0 mL for subcutaneous injection in a single use PFS and/or Autoinjector (AI)/Pen). The drug product in pre-filled syringe is manufactured by two sites (b) (4)
(b) (4) Amgen Inc., Thousand Oaks, CA (ATO), and Amgen Manufacturing Ltd. Juncos, Puerto Rico (AML). Autoinjector (AI)/Pen are assembled at AML. This inspection waiver memo is for the AML site only.

Facility Information



The following information is provided in support of waiving the pre-approval inspection:

- 1. The manufacturer does not hold an active U.S. license, or in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.*
AML facility at Juncos, Puerto Rico (FEI # 1000110364) is a multiproduct facility and will be manufacturing Evolocumab drug product in both PFS and AI/Pen presentations on approval of this submission. (b) (4)
(b) (4)
- 2. FDA has not inspected the establishment in the last 2 years.*
AML was inspected by BMAB with the district on March 24-28, 2014 and this Pre-Approval inspection for a PAS for (b) (4) was classified VAI. The SVS and TRP profiles are acceptable. The previous CGMP inspection performed on July 24-August, 2013 was VAI and BTP, CTX, GLA, SVS, and (b) (4) profiles were acceptable.
- 3. The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systematic problems, such as QC/QA oversight.*
Pre-Approval inspection performed by BMAB and the district on March 24-28, 2014 at AML was VAI and the CGMP inspection performed on July 24-August, 2013 was also VAI with acceptable profiles.

4. *The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.*

AML is approved as a multiple product facility and manufactures several commercial products.

5. *The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment. Point to consider:*

The manufacturing process for Evolocumab drug product-PFS and Pen at AML is substantially equivalent to other products manufactured in the same facility.

Signatures:

Lakshmi Rani Narasimhan, Ph.D, Microbiologist,
Biotech. Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality, Office of Compliance, CDER

Sang Bong Lee, Ph.D, Biologist,
Division of Monoclonal Antibodies, Office of Biotechnology Products, Office of Pharmaceutical Science

Clearance Routing

Peter Qiu, Ph.D.
Branch Chief, Biotech. Manufacturing Assessment Branch, Division of Good Manufacturing Practice Assessment, Office of Manufacturing and Product Quality, Office of Compliance, CDER

Kathleen Clouse, Ph.D.
Director, Division of Monoclonal Antibodies, Office of Biotechnology Products, Office of Pharmaceutical Science, CDER

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

/s/

LAKSHMI RANI NARASIMHAN
11/24/2014

SANG BONG LEE
11/24/2014

KATHLEEN A CLOUSE STREBEL
11/24/2014

ZHIHAO PETER QIU
11/24/2014



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: September 15, 2014

From: Lana Shiu, M.D.

General Hospital Devices Branch, DAGRID, ODE, CDRH

To: Kati Johnson

Division of Metabolism and Endocrine Product, Office of New Drugs, CDER

Via: Keith Marin and Ryan McGowan

Combination Products Team Leaders, GHDB, DAGRID, CDRH

Rick Chapman

Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH

Subject: BLA 125522 Evolocumab Prefilled Syringe and Auto-Injector /Applicant: Amgen
CDRH Tracking: ICC1400577

Indication: 1. Treatment of Primary Hyperlipidemia and Mixed Dyslipidemia

2. Treatment of Homozygous Familial Hypercholesterolemia (HoFH)

The PFS administers a single 1.0 mL (140 mg) fixed dose of evolocumab into subcutaneous (SC) tissue of the arm, abdomen, or thigh. It may be self-administered or administered by a caregiver or healthcare provider in a clinical or non-healthcare environment for user populations where the dose is approved.

The Autoinjector containing a glass PFS administers a single 1.0 mL (140 mg) fixed dose of evolocumab into subcutaneous (SC) tissue of the arm, abdomen, or thigh. It may be self-administered or administered by a caregiver or healthcare provider in a clinical or non-healthcare environment for user populations where the dose is approved.

Background:

Amgen is seeking approval for 2 device configurations:

1. Prefilled Glass Syringe with staked needle containing 140mg of Evolocumab/1mL
2. Autoinjector containing prefilled syringe (which is filled with 1mL of 140g Evolocumab)

The Evolocumab AI, containing 140 mg of Evolocumab solution for injection, is a pre-filled syringe (PFS) presentation that is administered via the functional secondary packaging (autoinjector) that serves as a drug delivery system for the product. The autoinjector is a single use, disposable drug product in which the functional secondary packaging components (the

(b) (4) are integrated with the current Evolocumab PFS, which is the primary container closure system for the product.

The subject AI is a modified version of the SureClick autoinjector which is currently approved and marketed for use with Enbrel (BLA 103795-sponsor is Amgen). Autoinjector front, rear and subassembly are manufactured by (b) (4)

Device Description—Prefilled Syringe (PFS)

The PFS is a prefilled, single-use, disposable, handheld drug delivery device for patients with mixed dyslipidemia and hypercholesterolemia. (b) (4)

For the 140 mg/mL prefilled syringe (PFS), the primary container closure consists of a 1 mL Type I glass syringe with a staked-in-place stainless steel needle covered with an (b) (4) needle shield and a (b) (4) (b) (4) plunger-stopper (b) (4)

The syringes are manufactured under the trade name (b) (4) by (b) (4) and the plunger-stoppers are manufactured under the trade name (b) (4) by (b) (4).

Dosage capability	Single dose: 1.0 mL of 140 mg/mL
Method of injection	Manual delivery
Packaging configuration	Prefilled Syringe – (b) (4) (b) (4) in a single carton.
Environment of use conditions	Non-Healthcare or Clinical Environments
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze.
Handling	Acclimate to room temperature by setting out at room temperature for 30 minutes. Keep in carton to protect from light.

3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Component	Parameter	Specification	Test Method
Syringe barrel with staked needle (b) (4)		(b) (4)	Manufacturer's certificate
			Measurement
			Measurement
			Measurement
			Manufacturer's certificate
			Manufacturer's certificate
Plunger-stopper			Manufacturer's certificate
			Manufacturer's certificate
			Measurement
			Measurement
Non-rigid needle shield			Manufacturer's certificate
			Tested

Shelf Life-No specific shelf life information was contained in the document reviewed.

Biocompatibility- (b) (4) syringe barrel is glass (b) (4) and the needle staked to the syringe is stainless steel which have been reviewed and approved for use previously. Syringe barrel in this product is made of (b) (4) which is surface contacting of limited duration per ISO 10993.

Test	Test Method Description	Acceptance Criteria	Test Results
Cytotoxicity	ISO 10993-5: Tests for Cytotoxicity – In vitro methods	Cytotoxicity according to ISO 10993-5 Section 8.5.	Pass
Sensitization	ISO 10993-10: Tests for Sensitization and Irritation	Sensitization according to ISO 10993-10 Section 7.5.6.	Pass
Irritation	ISO 10993-10: Tests for Sensitization and Irritation	Irritation according to ISO 10993-10 Section 7.5.6.	Pass

Sterility- (b) (4) sterilization of the glass barrel and (b) (4) sterilization of the plunger stopper.

Packaging- A labeled, single-use prefilled syringe is placed into a tray/blister pack with (b) (4) cover. Each tray is placed into a paperboard carton with its corresponding inserts. The carton protects the 140 mg/mL PFS from light.

Human Factors-LCDR Quynh-Nhu Nguyen of the Human Factor’s team is already consulted by DMEP.

Prefilled Syringe (PFS)- Functional Performance Testing

Test	Test Method Description	Test Article (Syringe, Plunger-stopper, Drug Product etc.)	Acceptance Criteria (AC) & Confidence Interval (CI)	Data Summary	Test Results	Report Number
Break loose and extrusion force (BLE)					PASS	RPT-048559: Verification Report: AMG 145 Prefilled Syringe Breakloose and Extrusion Testing of Evolocumab (AMG 145) at Operational Temperatures
Deliverable volume (DV)					PASS	RPT-051168: Verification Report: AMG145 Pre-filled Syringes Deliverable Volume Testing of Evolocumab (AMG 145) at Operational Temperatures
BLE at operating temperature – cold					PASS	RPT-048559: Verification Report: AMG 145 Prefilled Syringe Breakloose and Extrusion Testing of Evolocumab (AMG 145) at Operational Temperatures
BLE at operating temperature - room					PASS	RPT-048559: Verification Report: AMG 145 Prefilled Syringe Breakloose and Extrusion Testing of Evolocumab (AMG 145) at Operational Temperatures

Test	Test Method Description	Test Article (Syringe, Plunger-stopper, Drug Product etc.)	Acceptance Criteria (AC) & Confidence Interval (CI)	Data Summary	Test Results	Report Number
BLE at operating temperature - hot				(b) (4)	PASS	RPT-048559: Verification Report: AMG 145 Prefilled Syringe Breakloose and Extrusion Testing of Evolocumab (AMG 145) at Operational Temperatures
DV at operating temperature - cold					PASS	RPT-051168: Verification Report: AMG145 Pre-filled Syringes Deliverable Volume Testing of Evolocumab (AMG 145) at Operational Temperatures
DV at operating temperature - hot					PASS	RPT-051168: Verification Report: AMG145 Pre-filled Syringes Deliverable Volume Testing of Evolocumab (AMG 145) at Operational Temperatures
Packaging: transportation testing					PASS	RPT-048450: AMG 145 Pre Filled Syringe Packaging Distribution, and Device Functional Testing Verification Report
Post sterilization glide force					PASS	TA-007146: AMG 145 PFS Primary Container Performance Verification Report

Test	Test Method Description	Test Article (Syringe, Plunger-stopper, Drug Product etc.)	Acceptance Criteria (AC) & Confidence Interval (CI)	Data Summary	Test Results	Report Number	
Needle Shield Removal Force					(b) (4)	PASS	TA-007146: AMG 145 PFS Primary Container Performance Verification Report
Stress Cracking						PASS	TA-007146: AMG 145 PFS Primary Container Performance Verification Report

Review and Comments—Prefilled Syringe—Adequate/No issue:

Tests listed under prefilled syringe were comprehensive and results were acceptable without further issue.

Bench testing demonstrated acceptable dose accuracy showing the syringe is capable of delivering (b) (4) mL drug product (b) (4) when tested with 60 commercially representative prefilled syringes that were warmed to room temperature.

Batch/Lot	Component
Batch: 0010148230	PFS: Syringe Barrel/Needle, (b) (4) 1 mL (b) (4)
Batch: 0010148230	Plunger, (b) (4)
Lot: 0010136835	evolocumab at 140mg/mL

Further bench testing at non-standard operating temperatures (extreme cold and hot) should the combination product still delivered the drug product within expected dose accuracy.

Test	Mean	Max	Min	STDev	Units Tested	Acceptance Criteria (AC)	Target K Value	Actual K Value	Actual K \geq Target	Avg. \geq AC	All values \geq AC
Cold Temperature (5°C \pm 3°C)	(b) (4)								Pass	Pass	Pass
Hot Temperature (40° \pm 2°C)	(b) (4)								Pass	Pass	Pass

Device Description—Autoinjector

The AI/Pen 1.0 or 1.5 is a prefilled, single-use, disposable, handheld, mechanical (spring-based) injection device that is provided ready-to-use, pre-assembled with a prefilled syringe intended for patients with mixed dyslipidemia and hypercholesterolemia. The AI/Pen 1.0 or 1.5 delivers the complete dose in less than or equal to 15 seconds.

Amgen and (b) (4) developed the prefilled Autoinjector/Pen 1.5 (AI/Pen 1.5) on the basis of the existing SureClick AI/Pen (BLA 103795) that is marketed in the US and Canada for Enbrel (marketed under the name “Aranesp” in EU). The AI/pen 1.0 differs from the SureClick autoinjector in color, (b) (4)

Subsystem	Design Use			
	Enbrel AI/Pen 1.0	Aranesp AI/Pen 1.0	Evolocumab AI/Pen 1.0	Evolocumab AI/Pen 1.5
	Commercial	Commercial	Clinical Studies ^a Formative Human Factors Studies	Summative Human Factors Studies and Commercial configuration



One of the minor modifications as identified is (b) (4)

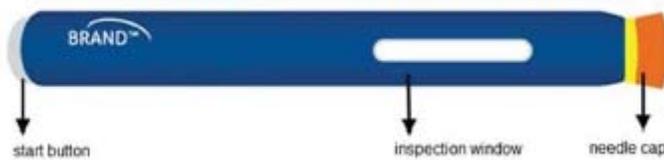
AI/Pen 1.0 and AI/Pen 1.5 Activation Sequence Modification

Device	Activation Sequence
AI/Pen 1.0	(b) (4)
AI/Pen 1.5	(b) (4)

Summary of Minor Functional Modifications and Related Tests

Subsystem	Change Description	Rationale	Test
Exterior components	(b) (4)	(b) (4)	Biocompatibility, Human Factors Study
Front Subassembly	(b) (4)	(b) (4)	Human Factors Study
Rear Sub-assembly	(b) (4)	(b) (4)	Verification Test

Figure 1. Autoinjector/Pen (AI/Pen 1.5)



Standards Utilized in the Development of Autoinjector

(b) (4)

Biocompatibility-Autoinjector

The assembled AI/Pen subassemblies integrate a prefilled syringe and; therefore, do not come into direct contact with the drug product. The AI/Pen 1.5 components that come into contact with the user during device handling/operation (skin contact) for limited duration.

Test	Test Method Description	Acceptance Criteria	Test Results
Cytotoxicity	ISO 10993-5: Tests for Cytotoxicity – In vitro methods	Cytotoxicity according to ISO 10993-5 Section 8.5.	Pass
Sensitization	ISO 10993-10: Tests for Sensitization and Irritation	Sensitization according to ISO 10993-10 Section 7.5.6.	Pass
Irritation	ISO 10993-10: Tests for Sensitization and Irritation	Irritation according to ISO 10993-10 Section 7.5.6.	Pass

Packaging-Autoinjector—Blister pack, (b) (4) topping, cardboard carton
Shelf life- Autoinjector (b) (4) months with accelerated aging to simulate 6 years

Performance Testing-Autoinjector

Test	Test Method & Acceptance Criteria			Test Results			
	Test Article	Test Method Description	Acceptance Sampling Plan & Rationale	Requirement	Data Summary	Results	Report Number
ENVIRONMENT/STORAGE/TRANSPORTATION TESTS							
Storage Temperature and Humidity 11608-1	(b) (4)					PASS	TRPT-024489
Operating Temperature and Humidity 11608-1						PASS	TRPT-024489
Transportation Shock & Vibration						PASS	RPT-048480

Test	Test Method & Acceptance Criteria				Test Results		
	Test Article	Test Method Description	Acceptance Sampling Plan & Rationale	Requirement	Data Summary	Results	Report Number
Subassembly Shelf-Life	(b) (4)					PASS	0051-021-TR-DVAATR-131122
Needle Extension						PASS	RPT-048480
Needle Cover Override Force						PASS	TRPT-023852

Test	Test Method & Acceptance Criteria				Test Results		
	Test Article	Test Method Description	Acceptance Sampling Plan & Rationale	Requirement	Data Summary	Results	Report Number
Shield Remover Removal Force	(b) (4)					PASS	TRPT-023852
Injection Activation Sequence						PASS	TRPT-023853
Injection Time Test						PASS	TRPT-024469
AlPan Free-fall Test 11605-1						PASS	TRPT-024471

Test	Test Method & Acceptance Criteria				Test Results		
	Test Article	Test Method Description	Acceptance Sampling Plan & Rationale	Requirement	Data Summary	Results	Report Number
AI/Pen Vibration Test 11608-1	(b) (4)					PASS	TRPT-024471
Activation Force Test						PASS	TRPT-023852
Needle Cover Pre-Injection Force Test						PASS	TRPT-023852
Plunger Spring Force Test						PASS	APPX-018816
Separation Force Test						PASS	TRPT-023852

Human Factors (Autoinjector)- LCDR Quynh-Nhu Nguyen of the Human Factor's team is already consulted by DMEP to review the validation studies regarding the changes in activation sequence of the AI.

Recommendation:

CDRH engineering review of the AI and its associated performance testing on the bench appears to be adequate (dose accuracy (b)(4) mL of drug product delivered under the specified time which is less than 15 sec with a mean time of delivery of (b)(4) sec). AI 1.0 was used during clinical trial and AI 1.5 will be the commercially distributed device constituent. They appear to differ in color (b)(4)

Although the engineer specifications for the (b)(4) are fine and the performance testing on the bench is also adequate, but the final validation testing is actually in the hands of the users. So I would defer to Human Factors/DMEPA review for the final safety and effectiveness determination.

Lana Shiu, M.D.

Lana L. Shiu - S

Digitally signed by Lana L. Shiu -S
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ou=FDA, ou=People, cn=Lana L. Shiu -S,
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Team Leader

Branch Chief



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