



**U.S. FOOD & DRUG  
ADMINISTRATION**

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

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**CBER SENTINEL PROGRAM SUFFICIENCY MEMORANDUM**

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**Through:** Azadeh Shoaibi  
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**To:** Meghna Alimchandani  
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**Subject:** CBER Sentinel Program Sufficiency Assessment

**Product:** HEMGENIX

**Sponsor:** CSL Behring, LLC

**STN:** BLA 125772/0

**Proposed Indication:** Treatment of adults with hemophilia B (congenital Factor IX deficiency)  
(b) (4)  
to reduce the frequency of bleeding episodes (b) (4)

**Approval Type:** ☒ Priority ☐ Standard review

**Submission Date:** Mar 24, 2022

**Action Due Date:** Nov 22, 2022

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**1. Objectives/Scope:**

This memo reviews the capability and sufficiency of the CBER active post-market risk identification and analysis system referred to as the CBER Sentinel Program to evaluate the serious risk for increased bleeding following HEMGENIX treatment in patients with high pre-treatment anti-AAV5 neutralizing antibody titers, in lieu of a safety post-market requirement (PMR) study under FDAAA<sup>1</sup>. The CBER Sentinel Program covers activities conducted through the contract with the Harvard Pilgrim Health Care Institute, the current and future contracts through the Biologics Effectiveness and Safety (BEST) Initiative, and the interagency agreement with the Centers for Medicare and Medicaid (CMS). Please see the STN 125772/0 OBPV/Division of Pharmacovigilance (DPV) review of the Pharmacovigilance Plan (PVP) for background on the serious risk for increased bleeding following HEMGENIX treatment in patients with high pre-treatment anti-AAV5 neutralizing antibody titers. HEMGENIX is a gene therapy product that uses the non-replicating, recombinant adeno-associated virus 5 (rAAV5) vector with an expression cassette encoding a codon-optimized coding DNA sequence of the Padua-variant (R338L) of the human factor IX (hFIXco-Padua) controlled by a liver specific promoter (LP1). Though the sponsor's proposed indication is for treatment of adults with hemophilia B (b) (4)

the anti-AAV5 antibody assay, that was used during clinical development, was determined (b) (4) The review team has determined the need for a safety postmarketing study to assess association of pre-treatment anti-AAV5 neutralizing antibody titers, using a validated anti-AAV5 assay, with annualized bleeding rate (ABR). Note that the study is dependent on the use of a validated anti-AAV5 assay.

**2. CBER Sentinel Program Sufficiency Assessment:**

Determination of the sufficiency of the CBER Sentinel Program to further characterize the serious risk of increased bleeding following HEMGENIX treatment in patients with high pre-treatment anti-AAV5 neutralizing antibody titers, was based on the following factors:

**2.1 Identification of exposure to HEMGENIX**

**2.2 Identification of the appropriate study population: Patients with hemophilia B (congenital Factor IX deficiency)**

<sup>1</sup> Under section 901 of the Food and Drug Administration Amendments Act (FDAAA), "The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B)."NOTE: The active post-market risk identification and analysis system under subsection (k)(3) refers to the Sentinel program.

<sup>2</sup> ISBT 128 is a global standard for the safe identification, accurate labeling, and efficient information transfer of medical products of human origin (including blood, cells, tissues, milk, and organ products) across disparate national and international health care systems.  
<https://www.iccbba.org/isbt-128-basics>

2.3 Characterization of occurrence of bleeding episodes in patients with known pre-treatment anti-AAV5 neutralizing antibody titers

2.4 Identification of exposure to comparator product: not applicable for this memo

## 2.1 Assessment for identification of exposure to HEMGENIX

### 2.1.1. Is the CBER Sentinel Program able to identify the product (exposure) of interest?

Please answer each question i – xi, including sub-questions.		Yes	No
i.	Is this the first or the only FDA-approved product for the indication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
ii.	Can the exposure be identified using a billing or reimbursement coding system? <i>If yes, check all that apply*</i> : <input type="checkbox"/> CPT <input type="checkbox"/> HCPCS <input checked="" type="checkbox"/> NDC <input type="checkbox"/> ICD <input type="checkbox"/> Other: [Coding system]	<input checked="" type="checkbox"/>	<input type="checkbox"/>
iii.	Is the ISBT 128 coding system <sup>2</sup> needed for the product identification?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
iv.	Can the reimbursement code of the product identify the brand name?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
v.	Is a history of uptake for previously approved products for the same indication needed? <i>If yes, list all products:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vi.	Is medical chart review needed to identify or validate the identification of this product?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vii.	Are claims data sources needed for exposure identification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
viii.	Are electronic health record (EHR) data sources needed for exposure identification?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
ix.	Are any other health record type data sources needed for exposure identification? <i>If yes, all health record types needed: [e.g., Registries, any other health records]</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
x.	Is product lot number needed for identification of this product?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
xi.	Is there a care setting of interest required for identification of this product? <i>If yes, check all that apply:</i>  <input type="checkbox"/> Inpatient <input type="checkbox"/> Outpatient <input type="checkbox"/> Emergency Room <input type="checkbox"/> Other: Hospitalization	<input type="checkbox"/>	<input checked="" type="checkbox"/>

\* At the time of this sufficiency memo submission, it is not confirmed if NDC codes to identify Hemgenic in claims databases will be available if approval is granted; however, if NDC codes are available, Hemgenix can be ascertained in claims databases via NDC.

### 2.1.2. Summary for product exposure identification

☒ Available data sources in the CBER Sentinel Program are *sufficient to identify the exposure of the product Hemgenix due to reasons identified in 2.1.1.ii, iv and vii* that support sufficiency.

☐ Available data sources in the CBER Sentinel Program are NOT sufficient to identify the exposure of the product due to reasons identified in [list all bullets from 2.1.1.i.—2.1.1.xi. that support insufficiency].

## 2.2. Assessment for identification of the appropriate study population: Patients with hemophilia B (congenital Factor IX deficiency)

### 2.2.1. Is the CBER Sentinel Program able to identify the study population of interest?

Please provide an answer for each question i – vi, including sub-questions.		Yes	No
i.	Does age need to be identified? <i>If yes, list the inclusion and exclusion criteria.. Check all that apply for the level of granularity in <input type="checkbox"/> Days <input type="checkbox"/> Months <input type="checkbox"/> Years</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
ii.	Does sex need to be identified? <i>If yes, list the inclusion [List the sex to be included] and exclusion criteria [List the sex to be excluded].</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
iii.	Does race need to be identified? <i>If yes, list the inclusion [List race to be included] and exclusion criteria [List race to be excluded]</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
iv.	Can the study population be identified in the data sources required for the exposure and outcome identification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
v.	Was this population previously identified within the CBER Sentinel Program activities?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vi.	Is there a requirement for linking mothers to their newborns in the data sources?	<input type="checkbox"/>	<input checked="" type="checkbox"/>

### 2.2.2. Summary for identification of study population

☒ Available data sources in the CBER Sentinel Program are *sufficient to identify the study population of interest* due to reasons identified in [list all bullets from 2.2.1.i.—2.2.1.vi. that support sufficiency].

☐ Available data sources in the CBER Sentinel Program are NOT sufficient to identify the study population of interest due to reasons identified in bullet [list all bullets from 2.2.1.i.—2.2.1.vi. that support insufficiency].

## 2.3 Assessment for characterization of occurrence of bleeding episodes following HEMGENIX treatment in patients with high pre-treatment anti-AAV5 neutralizing antibody titers

### 2.3.1 Is the CBER Sentinel Program able to identify the outcome(s) of interest?

Please provide an answer for each question i – xi, including sub-questions.		Yes	No
i.	Can the outcome of interest be identified using a billing or reimbursement coding system? If <u>yes</u> , check all that apply: <input type="checkbox"/> ICD <input type="checkbox"/> CPT <input type="checkbox"/> Other: Medical Record Review	<input type="checkbox"/>	<input checked="" type="checkbox"/>
ii.	Are there surrogate data elements or biomarkers that can assist to identify the outcome of interest? If <u>yes</u> , check all that apply: <input checked="" type="checkbox"/> Laboratory Test Results <input checked="" type="checkbox"/> Prescription drug <input checked="" type="checkbox"/> Order of lab test <input checked="" type="checkbox"/> Order of other diagnostic modalities <input type="checkbox"/> Other: [Data element/Biomarker]	<input checked="" type="checkbox"/>	<input type="checkbox"/>
iii.	Are there specific care settings in which this outcome is identified? If <u>yes</u> , check all that apply: <input type="checkbox"/> Inpatient <input type="checkbox"/> Outpatient <input type="checkbox"/> Emergency Room <input type="checkbox"/> Other: Hospitalization	<input type="checkbox"/>	<input checked="" type="checkbox"/>
iv.	Was this outcome previously identified within the CBER Sentinel Program activities? If <u>yes</u> , in what population was it used	<input type="checkbox"/>	<input checked="" type="checkbox"/>
v.	Is there a validated and acceptable algorithm available in the literature to identify the outcome of interest? If <u>yes</u> , list the PPV [PPV] and describe the population in which it was validated:	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vi.	Is a minimum follow-up time needed to identify the outcome of interest? If <u>yes</u> , what is the required follow-up period?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
vii.	Is medical chart review required to identify or validate the identification of the outcome?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
viii.	Is the prevalence of the outcome known? If <u>yes</u> , list background rates.	<input type="checkbox"/>	<input checked="" type="checkbox"/>
ix.	Are claims data sources needed for outcome characterization?	<input type="checkbox"/>	<input checked="" type="checkbox"/>
x.	Are electronic health record (EHR) data sources needed for outcome characterization?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
xi.	Are any other health record type data sources needed for outcome characterization? If <u>yes</u> , all health record types needed: [e.g., Registries, any other health records] –  Validated anti-AAV5 antibody assay that is not available at the time of this memo finalization	<input checked="" type="checkbox"/>	<input type="checkbox"/>

### 2.3.2 Summary of outcome characterization

☐ Available data sources in the CBER Sentinel Program are *sufficient to identify the outcome of bleeding episodes following HEMGENIX treatment in patients with high pre-treatment anti-AAV5 neutralizing antibody titers* due to reasons identified in [list all bullets from 2.3.1.i.—2.3.1.xi. that support sufficiency].

☒ Available data sources in the CBER Sentinel Program are NOT sufficient to identify the outcome of *bleeding episodes following HEMGENIX treatment in patients with high pre-treatment anti-AAV5 neutralizing antibody titers* due to reasons identified in [list all bullets from 2.3.1.i.—2.3.1.xi. that support insufficiency].

The study involves monitoring of reported bleeding in a lead-in period then an 18-month follow-up period, and to correlate with pre-treatment anti-AAV5 titers, based on a validated anti-AAV5 antibody assay, that is currently not available. CBER Sentinel Program does not collect biospecimens and does not have access to anti-AAV5 assay results if such testing is performed.

**2.4. Assessment for identification of exposure to comparator product:** not applicable.

**2.5. Is the CBER Sentinel Program able to identify the required comparator product? Respond to the questions below, if applicable.**

Please provide an answer for each question i – xi, including sub-questions		Yes	No
<b>i.</b>	Is a comparator product needed for the assessment? If no, skip to section III for Recommendation. If yes, list all products:	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<b>ii.</b>	Can the comparator product be identified using a billing reimbursement code? If yes, check all that apply: <input type="checkbox"/> CPT <input type="checkbox"/> HCPCS <input type="checkbox"/> NDC <input type="checkbox"/> ICD <input type="checkbox"/> Other:[Billing reimbursement code]	<input type="checkbox"/>	<input type="checkbox"/>
<b>iii.</b>	Can the comparator product be exclusively identified using the billing reimbursement codes?	<input type="checkbox"/>	<input type="checkbox"/>
<b>iv.</b>	Is the ISBT 128 coding system <sup>2</sup> needed for the comparator product identification?	<input type="checkbox"/>	<input type="checkbox"/>
<b>v.</b>	Can the reimbursement code of the comparator product identify the brand name?	<input type="checkbox"/>	<input type="checkbox"/>
<b>vi.</b>	Is medical chart review needed to identify or validate the identification of this comparator product?	<input type="checkbox"/>	<input type="checkbox"/>
<b>vii.</b>	Are claims data sources needed for exposure identification of the comparator product?	<input type="checkbox"/>	<input type="checkbox"/>
<b>viii.</b>	Are electronic health record (EHR) data sources needed for exposure identification of the comparator product?	<input type="checkbox"/>	<input type="checkbox"/>

Please provide an answer for each question i – xi, including sub-questions		Yes	No
<b>ix.</b>	Are any other health record type data sources needed for exposure identification of the comparator product? If yes, list all health record types needed: [e.g., Registries, any other health records]	<input type="checkbox"/>	<input type="checkbox"/>
<b>x.</b>	Is product lot number needed for identification of this comparator product?	<input type="checkbox"/>	<input type="checkbox"/>
<b>xi.</b>	Is there a care setting of interest for identification of this comparator product? If yes, check all that apply: <input type="checkbox"/> Inpatient <input type="checkbox"/> Outpatient <input type="checkbox"/> Emergency Room <input type="checkbox"/> Other: Hospitalization	<input type="checkbox"/>	<input type="checkbox"/>

### 2.5.1. Summary for comparator exposure identification

- ☐ Available data sources in the CBER Sentinel Program are sufficient to identify the comparator product due to reasons identified in [list all bullets from 2.4.1.i.—2.4.1.xi. that support sufficiency].
- ☐ Available data sources in the CBER Sentinel Program are NOT sufficient to identify the comparator product due to reasons identified in [list all bullets from 2.4.1.i.—2.4.1.xi. that support insufficiency].

### 3. Recommendation:

- ☐ The CBER Sentinel Program is *sufficient* to assess the serious risk of [describe] associated with [product] at this time. [Summarize all bullets 2.1.—2.4. that support sufficiency]
- ☒ The CBER Sentinel Program is NOT sufficient to assess the serious risk for increased bleeding following HEMGENIX treatment in patients with high pre-treatment anti-AAV5 neutralizing antibody titers, in lieu of a PMR study under FDAAA. The assessment for this serious risk involves measurement of anti-AAV5 titers using a validated assay (currently not available), and the monitoring of reported bleeding in a lead-in period then an 18-month follow-up period. CBER Sentinel data sources are unable to identify outcomes which require patient-level serology testing, and development of validated assay. The follow-up period needed for this type of study is also too long to assure that the patient will stay with the same insurance company to have his/her data captured in the CBER Sentinel databases.