CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761133Orig1s000

PROPRIETARY NAME REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From:

Carlos M Mena-Grillasca, BS Pharm
Biologics Suffix Specialist, DMAMES/OMEPRM/OSE

Through:

Irene Z Chan, PharmD, BCPS
Acting Director, Division of Medication Error Prevention and Analysis I/OMEPRM/OSE

Subject: Re-assessment of the nonproprietary name for BLA 761133

Regulatory History:

Takeda Pharmaceuticals U.S.A., Inc. (Takeda) submitted a Biologics License Applications (BLA 761133) pursuant to Section 351(a) of the Public Health Service Act for Entyvio (vedolizumab) injection for subcutaneous administration. Takeda is also the license holder for BLA 125476, Entyvio (vedolizumab) for injection for intravenous administration, approved on May 20, 2014.

On December 13, 2019 DMEPA determined that a suffix would not be designated for BLA 761133. Therefore, vedolizumab would be the proper name designated in the license[a].

[a] Merchant, L. Memorandum: Evaluation of the Nonproprietary Name for BLA 761133. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Dec 13.

Re-assessement:

We maintain our previous determination that a different nonproprietary name for BLA 761133 would not be designated in this particular case. Thus, BLA 761133 can be managed under the same nonproprietary name, vedolizumab, as BLA 125476.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

IRENE Z CHAN
08/07/2023 11:25:29 AM

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Public Health Service
Food and Drug Administration
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/s/

IRENE Z CHAN
08/02/2023 11:50:00 AM

PROPRIETARY NAME REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 Review:	June 15, 2023
Application Type and Number:	BLA 761133
Product Name and Strength:	Entyvio(vedolizumab)[a] injection, 108 mg/0.68 mL Entyvio Pen (vedolizumab)[a] injection, 108 mg/0.68 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Takeda Development Center Americas, Inc. (Takeda)
PNR ID #:	2023-1044725057
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.
DMEPA 1 Director (Acting):	Irene Z. Chan, Pharm.D., BCPS

[a]The proper name 'vedolizumab' has an exception from the Biologics suffix requirement.
Merchant, L. Memo for Evaluation of the Nonproprietary Name Through CDER Director (BLA761133). Silver Spring(MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 13.

Contents

1 INTRODUCTION

This review evaluates the proposed proprietary name, Entyvio and Entyvio Pen, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed proprietary name are outlined in the reference section and Appendix A, respectively. Takeda did not submit an external name study for these proposed proprietary names.

1.1 REGULATORY HISTORY

The proprietary name Entyvio was approved on May 20, 2014 for vedolizumab 300 mg per vial, lyophilized cake for intravenous infusion for the indications of adult ulcerative colitis (UC) and adult Crohn's disease (CD).[b] On February 12, 2019, Takeda submitted a request for proprietary name review under IND 118980 for the proposed proprietary names, (b) (4) and Entyvio Pen, for a new dosage form, injection, intended for subcutaneous injection. The proposed dosage form would be available in a 108 mg/0.68 mL prefilled syringe and autoinjector. On March 7, 2019, the proprietary name request for (b) (4) and Entyvio Pen, was submitted under BLA 761133. On August 7, 2019, Takeda submitted an amendment to IND 118980 and BLA 761133 to revise the proposed name for their prefilled syringe presentation from (b) (4) to Entyvio.

On August 8, 2019, we conditionally approved the proprietary name Entyvio for the prefilled syringe presentation and Entyvio Pen for the prefilled pen presentation in OSE review 2019-29312270 and 2019-29348539.[c] On December 17, 2019, BLA 761133 received a complete response (CR) due to product quality/manufacturing, device, and human factors deficiencies.

Thus, Takeda resubmitted the name, Entyvio and Entyvio Pen, for review under BLA 761133 on March 27, 2023.

1.2 PRODUCT INFORMATION

The following product information is provided in the proprietary name submission and prescribing information submitted on March 27, 2023 under BLA 761133.

[b]Khosla, L. Proprietary Name Review for Entyvio (IND 9125/BLA 125476). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 AUG 19. OSE RCM No.: 2013-590

[c]Abraham, S. Proprietary Name Review for Entyvio and Entyvio Pen (IND 118980 and BLA 761133). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 8. OSE Panorama #s: 2019-29312270 and 2019-29348539

Table 1. Relevant Product Information for Entyvio (vedolizumab) intravenous and prefilled syringe and Entyvio Pen (vedolizumab)

Product Name	Entyvio[d] BLA 125476	Entyvio BLA 761133	Entyvio Pen BLA 761133
Initial Approval Date	May 20, 2014	N/A	N/A
Proper name	Vedolizumab[a]		
Intended Pronunciation	en tye' vee oh	en tye' vee oh	en tye' vee oh Pen
Route of Administration	Intravenous	Subcutaneous	
Indication	Entyvio (b) (4) is indicated in adults for the treatment of a)moderately to severely active ulcerative colitis b)moderately to severely active Crohn's disease.	Entyvio (b) (4) and Entyvio Pen is for the maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC).[e]	
Dosage Form	For injection	Injection	
Strength	300 mg per vial	108 mg/0.68 mL	
Dose and Frequency	Recommended dosage in UC and CD: 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter.	SC Injection: 108 mg every two weeks (Q2W) for maintenance treatment following at least two intravenous infusions of Entyvio (vedolizumab) injection for intravenous use.	
How Supplied	Entyvio (vedolizumab) for injection is supplied as a sterile, white to off-white, preservative-free, lyophilized cake for intravenous infusion: 300 mg single-dose vial in individual carton	Prefilled Syringe- 108 mg/0.68 single-dose prefilled syringe in an individual carton The single-dose, disposable ENTYVIO prefilled syringe is comprised of a 1 mL long glass syringe with a fixed 27 gauge thin wall, ½ inch needle. The syringe has a rubber needle cover encased in a plastic shell and rubber stopper. The	Prefilled Pen - 108 mg/0.68 single-dose prefilled pen in an individual carton The single-dose, disposable ENTYVIO prefilled pen (ENTYVIO Pen) is comprised of a 1 mL long glass syringe with a fixed 27 gauge thin wall, ½ inch needle. The syringe has a rubber needle cover encased in a plastic shell and

[d] Entyvio Prescribing Information. Dailymed. Accessed April 20, 2023. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6e94621c-1a95-4af9-98d1-52b9e6f1949c.

[e] In BLA 761133, the Applicant proposes the Entyvio (prefilled syringe) and Entyvio Pen presentations for maintenance treatment of adult patients with moderately to severely active Ulcerative Colitis (UC). Resubmission Cover Letter. BLA 761133. 2023 March 27. \\CDSESUB1\EVSPROD\bla761133\0051\m1\us\cover-letter.pdf

APPEARS THIS WAY ON ORIGINAL

		syringes are not made with natural rubber latex.	rubber stopper. The syringes are not made with natural rubber latex.
Storage	Refrigerate ENTYVIO unopened vials, prefilled syringes, and prefilled pens at 2ºC to 8ºC (36º to 46ºF).		
		If needed, the ENTYVIO prefilled syringe or ENTYVIO Pen can be left out of the refrigerator in original package at room temperature up to 25°C (77ºF) for up to 7 days (for example, when traveling). Do not use ENTYVIO prefilled syringe or ENTYVIO Pen if left out of the refrigerator for more than 7 days.	

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name, Entyvio and Entyvio Pen.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that Entyvio and Entyvio Pen would not misbrand the proposed product. The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) concurred with the findings of OPDP's assessment for Entyvio and Entyvio Pen. The Division of Gastroenterology (DG) concurred with the findings of OPDP's assessment for Entyvio and Entyvio Pen.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the proposed proprietary name, Entyvio and Entyvio Pen.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proposed proprietary names[f].

[f] USAN stem search conducted on April 11, 2023.

2.2.2 Components of the Proposed Proprietary Name

The proprietary name Entyvio, for the prefilled syringe presentation, is comprised of a single word that does not contain any components (i.e. a modifier, route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

The proprietary name Entyvio Pen, for the autoinjector presentation, is comprised of a single word followed by the modifier, "Pen" and does not contain any other components (i.e. route of administration, dosage form, etc.) that are misleading or can contribute to medication error.

2.2.3 Comments from Other Review Disciplines at Initial Review

On April 25, 2023, the Division of Gastroenterology (DG) did not forward any comments or concerns relating to Entyvio and Entyvio Pen at the initial phase of the review.

2.2.4 FDA Name Simulation Studies

Ninety (n=90) practitioners participated in DMEPA's prescription studies for Entyvio. Ninety-five (n=95) practitioners participated in DMEPA's prescription studies for Entyvio Pen. One CPOE participant selected Entyvio from a "dynamic contains" pick list. The participant typed "Entyvio" and selected "Entyvio" from the dropdown menu instead of selecting Entyvio Pen. Additionally, two inpatient participants misinterpreted 'Entyvio Pen' as 'Entyvio'. We acknowledge that omission and oversight of a modifier is cited in literature as a common cause of medication error.[g] The use of the modifier, "Pen", in Entyvio Pen was previously evaluated.[b]

Appendix B contains the results from the prescription simulation studies.

2.2.5 Safety Assessment of the Proposed Names Entyvio and Entyvio Pen

The use of the root name Entyvio, the use of the root name Entyvio for the prefilled syringe presentation, and Entyvio Pen, were evaluated in the previous review,[b] and our previous determination is unchanged.

2.2.6 Communication of DMEPA's Determination

On June 15, 2023, DMEPA 1 communicated our determination to the Division of Gastroenterology (DG).

3 CONCLUSION

The proposed proprietary names, Entyvio and Entyvio Pen, are conditionally acceptable.

If you have any questions or need clarifications, please contact Alvis Dunson, OSE project manager, at 301-796-6400.

3.1 COMMENTS TO TAKEDA DEVELOPMENT CENTER AMERICAS, INC.

[g] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. J Gen Intern Med. 2002; 17(8): 579-587.

We have completed our review of the proposed proprietary names, Entyvio and Entyvio Pen, and have concluded that these names are conditionally acceptable.

If any of the proposed product characteristics as stated in your submission, received on March 27, 2023, are altered prior to approval of the marketing application, the names must be resubmitted for review.

4 REFERENCES

1. USAN Stems (https://www.ama-assn.org/about/united-states-adopted-names-approved-stems)

USAN Stems List contains all the recognized USAN stems.

2. Phonetic and Orthographic Computer Analysis (POCA)

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther_biological).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (http://www.nlm.nih.gov/research/umls/rxnorm/overview.html).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. Misbranding Assessment: For prescription drug products, OPDP assesses the name for misbranding concerns. For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. Safety Assessment: The safety assessment is conducted by DMEPA, and includes the following:

a. Preliminary Assessment: We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [h]

[h] National Coordinating Council for Medication Error Reporting and Prevention. https://www.nccmerp.org/about-medication-errors Last accessed 10/05/2020.

*Table 2- Prescreening Checklist for Proposed Proprietary Name

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@FDA,

Cerner RxNorm, and names in the review pipeline using a 55% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:

- Highly similar pair: combined match percentage score ≥70%.
- Moderately similar pair: combined match percentage score ≥55% to ≤ 69%.
- Low similarity: combined match percentage score ≤54%.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names are further evaluated to identify the presence of attributes that are known to cause name confusion.
    - Name attributes: We note that the beginning of the drug name plays a significant role in contributing to confusion. Additionally, drug name pairs that start with the same first letter and contain a shared letter string of at least 3 letters in both names are major contributing factor in the confusion of drug names7F[i]. We evaluate all moderately similar names retrieved from POCA to identify the above attributes. These names are further evaluated to identify overlapping or similar strengths or doses.
    - Product attributes: Moderately similar names of products that have overlapping or similar strengths or doses represent an area for concern for FDA. The dose and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and the information can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form) may be limited when the strength

[i] Shah, M, Merchant, L, Characteristics That May Help in the Identification of Potentially Confusing Proprietary Drug Names. Therapeutic Innovation & Regulatory Science, September 2016

or dose overlaps. DMEPA reviews such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).

- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

   Four separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions, verbal pronunciation of the drug name or during computerized provider order entry. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify vulnerability of the proposed name to be misinterpreted by healthcare practitioners during written, verbal, or electronic prescribing.

   In order to evaluate the potential for misinterpretation of the proposed proprietary name during written, verbal, or electronic prescribing of the name, written inpatient medication orders, written outpatient prescriptions, verbal orders, and electronic orders are simulated, each consisting of a combination of marketed and unapproved drug products, including the proposed name.

d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

   The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name.

   Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is ≥ 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a common strength or dose.			
Orthographic Checklist		Phonetic Checklist	
Y/N	Do the names begin with different first letters? *Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.*	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? **FDA considers the length of names different if the names differ by two or more letters.*	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		

Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is **≥55%** to **≤69%).**

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation. For single strength products, also consider circumstances where the strength may not be expressed. For any i.e., drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components. To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion: • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.

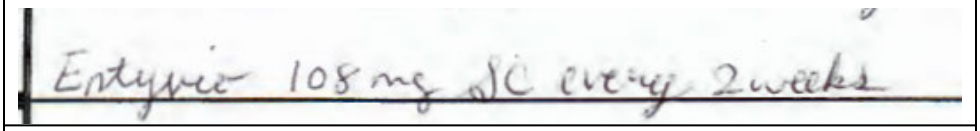
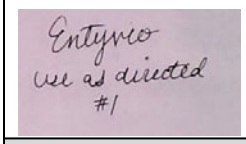
	Orthographic Checklist (Y/N to each question)	Phonetic Checklist (Y/N to each question)
	• Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. • Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. • Considering variations in scripting of some letters (such as *z* and *f*), is there a different number or placement of upstroke/downstroke letters present in the names? • Is there different number or placement of cross-stroke or dotted letters present in the names? • Do the infixes of the name appear dissimilar when scripted? • Do the suffixes of the names appear dissimilar when scripted?	• Do the names have different number of syllables? • Do the names have different syllabic stresses? • Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion? • Across a range of dialects, are the names consistently pronounced differently?

Table 5: Low Similarity Name Pair Checklist (i.e., combined score is **≤54%).**

Names with low similarity are generally acceptable unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Entyvio Study (Conducted on March 31, 2023)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  	Entyvio Use as directed #1
Outpatient Prescription:  	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Entyvio	

FDA Prescription Simulation Responses (Aggregate Report)

258 People Received Study

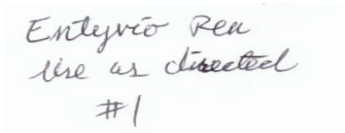
90 People Responded

Study Name: Entyvio

Total	22	25	20	23	
INTERPRETATION	INPATIENT	CPOE	VOICE	OUTPATIENT	TOTAL
ANTEVIO	0	0	1	0	1
ANTIVIO	0	0	2	0	2
ENTEYVIO	0	0	0	1	1
ENTIBIO	0	0	1	0	1
ENTIVEO	0	0	1	0	1
ENTIVIO	0	0	6	0	6

ENTYVEO	0	0	0	6	6
ENTYVIC	2	0	0	0	2
ENTYVIE	3	0	0	0	3
ENTYVIO	14	25	7	16	62
ERTYVIE	1	0	0	0	1
ERTYVIO	1	0	0	0	1
ESTYVIE	1	0	0	0	1
NETIVIO	0	0	1	0	1
PENTIVIO	0	0	1	0	1

Figure 2. Entyvio Pen Study (Conducted on April 4, 2023)

Handwritten Medication Order/Prescription	Verbal Prescription
Medication Order:  	Entyvio Pen Use as directed #1
Outpatient Prescription:  	
CPOE Study Sample (displayed as sans-serif, 12-point, bold font)	
Entyvio Pen	

FDA Prescription Simulation Responses (Aggregate Report)

258 People Received Study

85 People Responded

Study Name: Entyvio Pen

Total	20	23	23	19	
INTERPRETATION	INPATIENT	CPOE	VOICE	OUTPATIENT	TOTAL
AMTIVIO PEN	0	0	1	0	1
ANTIVIO	0	0	1	0	1
ANTIVIO PEN	0	0	1	0	1
ENTEJVIO	0	0	0	1	1
ENTEJVIO PEN	0	0	0	1	1
ENTENVIO PEN	0	0	1	0	1
ENTIFVIO PEN	0	0	1	0	1
ENTIVEO PEN	0	0	1	0	1
ENTIVIO PEN	0	0	6	0	6
ENTYNIO PEN	1	0	0	0	1
ENTYVIA PEN	2	0	0	0	2
ENTYVIO	2	1	0	0	3
ENTYVIO PEN	13	22	9	11	55
ENTYVIO PEN 108MG	1	0	0	0	1
ENTYVIO REA	0	0	0	2	2
ENTYVIO REU	0	0	0	4	4
ENTYVIS PEN	1	0	0	0	1
INACTIVO PEN	0	0	1	0	1
INTIVIO PEN	0	0	1	0	1

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHERLY ABRAHAM
06/15/2023 11:15:22 AM

IDALIA E RYCHLIK
06/20/2023 09:17:33 AM

IRENE Z CHAN
06/20/2023 04:52:30 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

FROM: Lubna Merchant, M.S., PharmD.
Acting Director, DMEPA
Deputy Director, OMEPRM
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Lubna I. Merchant -S
Digitally signed by Lubna I. Merchant -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=200039 4735, cn=Lubna I. Merchant -S
Date: 2019.12.13 10:07:29 -05'00'

THROUGH: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

Janet Woodcock -S
Digitally signed by Janet Woodcock -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Janet Woodcock -S, 0.9.2342.19200300.100.1.1=2000092018
Date: 2019.12.13 10:26:26 -05'00'

SUBJECT: Evaluation of the nonproprietary name for BLA 761133.

TO: BLA 761133

Takeda Pharmaceuticals submitted a new Biologics License Application (BLA 761133) pursuant to Section 351(a) of the Public Health Service Act, for a liquid formulation[1] of a currently approved biological product: Entyvio (vedolizumab) (BLA 125476).

Entyvio (vedolizumab) is currently approved for the treatment of adult patients with moderately to severely active Ulcerative Colitis (UC) and Crohn's Disease (CD) and supplied in a vial as a lyophilized powder[2] (300 mg) that requires reconstitution before being administered intravenously in a health care setting only. Takeda is the license holder for BLA 125476 and applicant for BLA 761133.

The new formulation in BLA 761133 is to be administered subcutaneously via a single-use, prefilled syringe (PFS) or an autoinjector (AI). Per Takeda, the proposed liquid formulation of vedolizumab is intended to provide patients with UC the option to switch from IV

[1] The official USP recognized dosage form for the proposed formulation is *Injection*

[2] The official USP recognized dosage form for the proposed formulation is *for Injection*

infusions to self-administered subcutaneous (SC) injections once they are in the maintenance phase of their treatment course. This new marketing application for liquid vedolizumab cross references BLA 125476.

Under FDA's prescription drug user fee bundling policy, different dosage forms should be submitted in separate original applications unless the products are quantitatively and qualitatively identical (drugs) or alike (biological products) in composition.[3] After reviewing the compositions of lyophilized and liquid vedolizumab, OBP determined that these biological products are quantitatively and qualitatively alike for user fee purposes. Takeda was advised that the proposed liquid formulation of vedolizumab, to be administered via an AI or PFS, may be submitted as a supplement to the approved BLA 125476 for Entyvio.

However, Takeda noted that they had already formatted the submission as a new BLA and were planning on filing it shortly as a new BLA. Takeda subsequently submitted this formulation as a new BLA. Takeda is proposing to have a single U.S. prescribing information (USPI) for vedolizumab that would include all approved products (i.e., lyophilized powder in a vial, liquid vedolizumab in an AI or PFS) and include all approved indications. Takeda is also proposing to have the same root proprietary name, Entyvio, for the two formulations, with the addition of the modifier *Pen* (for the AI).

FDA issued a final guidance entitled Nonproprietary Naming of Biological Products on January 13, 2017 stating the Agency's intention to designate proper names that include four-letter distinguishing suffixes for biological products.[4] This 351(a) application (BLA 761133) is within the scope of this guidance.

The currently approved formulation for Entyvio (BLA 125476) is also within the scope of the guidance; the draft update guidance, issued in March 2019, addresses nonproprietary names of biological products licensed under section 351(a) that do not include an FDA-designated suffix[5]. The updated guidance, if finalized, will explain that FDA does not expect the nonproprietary names of such products to be revised in order to accomplish the objectives of the naming convention described in the January 2017 final guidance for industry.

We carefully considered whether the nonproprietary name of the new proposed liquid formulation in BLA 761133 should include a suffix or whether the proper name considerations for this product warrant departing from the January 2017 final guidance. Among the factors we have considered are the following:

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[3] See the recommendations in section III.A.3 of Guidance for Industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (Dec. 2004), available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf

[4] Available at https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf (hereafter "naming guidance").

[5] Available at https://www.fda.gov/media/121316/download

1. Based on Office of Biotechnology Products' evaluation[6], the drug substance in the approved formulation and the proposed formulation are essentially unchanged with respect to product quality attributes. The same reference standard is used for the characterization, release and stability testing of the drug substance and drug product in the liquid and lyophilized formulations.

2. The vedolizumab drug substance in the liquid and lyophilized formulations share the same upstream manufacturing process. Differences in upstream manufacturing processes drive most post-translational modifications that could cause changes in critical quality attributes or potency of a drug substance; but here, the manufacture of the liquid formulation follows the same upstream process as the lyophilized formulation. The drug substance downstream manufacturing processes are identical until the (b) (4) (b) (4) Vedolizumab liquid is formulated at a higher concentration (160 mg/mL compared to 60 mg/mL) with (b) (4) polysorbate 80 (b) (4) and no sucrose. All other excipients in the vedolizumab liquid formulation are alike compared to the vedolizumab lyophilized formulation. The DS container closures are made of different materials.

3. There are slight differences in the drug substance stability only under accelerated conditions (not under storage conditions). These differences may be attributed to differences in concentration and excipients.

4. We note that the dose (300 mg vs. 108 mg) and the route of administration (intravenous vs. subcutaneous) differ between the two formulations. However, the indicated patient populations are intended to be the same for both the currently approved lyophilized powder formulation and this proposed liquid formulation of vedolizumab. The proposed liquid formulation of vedolizumab is intended to provide patients with UC the option to switch from IV infusions to self-administered SC injections once they are in the maintenance phase of their treatment course.

5. We noted above that this change could also be managed under a supplement to the current BLA, which would not have resulted in a change to the proper name under the approach to nonproprietary naming described in the final guidance. In fact, after reviewing the compositions of lyophilized and liquid vedolizumab, the Agency determined that these biological products are quantitatively and qualitatively alike for user fee purposes. Therefore, FDA advised Takeda to submit the proposed liquid

[6] Wilson W. CMC Executive Summary. BLA 761133.001 Silver Spring (MD): FDA, CDER, OPQ, OBP (US); 2019 December 2.

formulation of vedolizumab as a supplement to BLA 125476. However, Takeda, decided to submit this formulation as a new BLA.

Takeda is proposing to have a single USPI for vedolizumab that would include both the lyophilized powder and liquid vedolizumab formulations and include all approved indications. Takeda is proposing to have the same root proprietary name, Entyvio, for the two formulations, with the addition of the modifier *Pen* (for the AI). The naming convention of using the same root proprietary name for different dosage forms is generally found acceptable. We have not identified any safety or misbranding concerns that would render the root proprietary name, Entyvio, unacceptable for this liquid formulation.

6. As noted in the final naming guidance, distinguishing nonproprietary names will facilitate pharmacovigilance when other means to track a specific dispensed product are not readily accessible or available; facilitate accurate identification of these biological products by health care practitioners and patients; and help prevent inadvertent substitution that may lead to medication errors. As the guidance explains, a distinguishing suffix supports the tracking of product-specific events over time, our ability to track adverse events to a specific manufacturer (and as appropriate, to a lot or manufacturing site for a particular biological product), and our ability to detect safety signals throughout the life cycle of a product so that the Agency and the manufacturer can act swiftly and in a targeted manner to identify and address a problem. As noted above, the drug substance proposed in this submission, vedolizumab, is essentially unchanged with respect to product quality attributes. Accordingly, we think it is highly unlikely that the two formulations of Entyvio would have different immunogenicity profiles. Also, as noted above, Takeda is the license holder for BLA 125476 and the Applicant for BLA 761133 and the two products will be marketed under the same root proprietary name, Entyvio. While this may cause some increased risk of a patient not receiving the intended presentation, this does not outweigh the risk that the inclusion of a suffix in the nonproprietary name for the liquid formulation (but not in the nonproprietary name of the lyophilized powder formulation) may create confusion. Specifically, health care practitioners or patients could interpret the different nonproprietary names to mean that the drug substances in the products are different.

Given the above factors, a suffix would not be designated in this particular case. The addition of a suffix to the nonproprietary name of the liquid formulation[7] of Entyvio, while not adding the suffix to the lyophilized powder formulation of Entyvio, could create confusion and would not further the goals of the naming convention.

This memorandum documents the justification for and supervisory concurrence with the decision to depart from the recommendations in the January 2017 final naming guidance in

[7] The official USP recognized dosage form for the proposed formulation is Injection.

approving a nonproprietary name without a suffix for this product.[8] We based this determination upon consideration of all the factors outlined above for this BLA. If any of the factors enumerated above were to change, we may reconsider the appropriate proper name format for this BLA. The following comments will be communicated to Takeda in an advice letter.

Comments for Takeda Pharmaceuticals

We acknowledge that the agency previously notified you that your proposed BLA is within the scope of the naming guidance[9] and that FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA. However, we have determined that a suffix will not be designated for this proposed product. Therefore, vedolizumab will be the proper name designated in the license should your 351(a) BLA be approved during this review cycle.

[8] See 21 C.F.R. § 10.115(d)(3) ("Although guidance documents do not legally bind FDA, they represent the agency's current thinking. Therefore, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence.").

[9] Available at https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf

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/s/

LUBNA A MERCHANT
12/13/2019 10:49:41 AM