

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761064Orig1s000

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME 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:	March 9, 2017
Application Type and Number:	BLA 761064
Product Name and Strength:	Rituxan Hycela (rituximab and hyaluronidase) Injection 1,400 mg rituximab and 2,000 units/mL hyaluronidase per 11.7 mL solution 1,600 mg rituximab and 2,000 units/mL hyaluronidase per 13.4 mL solution
Total Product Strength:	1,400 mg and 23,400 units 1,600 mg and 26,800 units
Product Type:	Multi-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genentech
Panorama #:	2016-11908455
DMEPA Primary Reviewer:	Leeza Rahimi, Pharm.D.
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1 INTRODUCTION

This review evaluates the proposed proprietary name, Rituxan Hycela***, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant submitted an external name study, conducted by (b) (4), for this product.

1.1 REGULATORY HISTORY

Rituxan (rituximab) was initially approved on November 26, 1997 for intravenous administration available in two different strengths of 500 mg/50 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL) single dose vials. On August 26, 2016, the Sponsor for Rituxan submitted the name (b) (4)*** for their subcutaneous multi-ingredient formulation of rituximab and hyaluronidase with two proposed strengths of: 1,400 mg rituximab and 23,400 units hyaluronidase, and 1600 mg rituximab and 26,800 units of hyaluronidase solution under BLA 76064.. However, OPDP objected to the proposed proprietary name and thus it was found unacceptable by DMEPA under OSE # (b) (4) dated November 07, 2016.^a

Thus, the Applicant submitted the name, Rituxan Hycela***, for review on December 13, 2016.

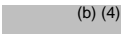
1.2 PRODUCT INFORMATION

The following product information for **Rituxan Hycela** is provided in the December 13, 2016 proprietary name submission.

Table 1. Product Characteristics of Rituxan and Rituxan Hycela		
	Rituxan Hycela (proposed)	Rituxan
Active Ingredient	Rituximab/hyaluronidase	Rituximab
Indication	Follicular Lymphoma (FL), Diffuse Large B-Cell Lymphoma (DLBCL) and Chronic Lymphocytic Leukemia (CLL).	Non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), Rheumatoid Arthritis (RA), Wegner Granulomatosis (WG) with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids
Route of Administration	Subcutaneous	Intravenous
Strength	1400 mg rituximab and 2000 units/mL hyaluronidase per 11.7 mL	100 mg/10 mL 500 mg/50 mL

^a Rahimi, L. Proprietary Name Review for (b) (4) BLA 761064. Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2016 Nov 07. RCM No.: (b) (4)

	• 1600 mg rituximab and 2000 units/mL hyaluronidase per 13.4 mL	
Dose and Frequency	<u>FL</u> (b) (4) <i>Relapsed or Refractory, Follicular Lymphoma</i> • Administer once weekly for 3 weeks following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total). <i>Retreatment for Relapsed or Refractory, Follicular Lymphoma</i> • Administer once weekly for 3 weeks following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total). <i>Previously Untreated, Follicular Lymphoma</i> • Administer on Day 1 of Cycles 2-8 of chemotherapy, for up to 7 cycles following a full intravenous Rituxan dose on Day 1 of Cycle 1 of chemotherapy. <i>Non-progressing, Follicular Lymphoma after the first line CVP chemotherapy</i> • Following completion of 6-8 cycles of CVP chemotherapy, administer once weekly for 3 weeks following a full intravenous Rituxan dose at week 1 (i.e. 4 weeks in total), at 6 month	<u>CLL</u> 375 mg/m² in the first cycle and 500 mg/m² in cycles 2-6, in combination with FC, administered every 28 days <u>NHL</u> (b) (4) <u>RA</u> In combination with methotrexate and glucocorticoids is two-1000 mg separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. <u>WG</u> Dose for WG and MPA in combination with glucocorticoids is 375 mg/m² once weekly for 4 weeks

	intervals to a maximum of 16 doses. <u>DLBCL</u> •  (b) (4) <u>CLL</u>  (b) (4)	
Dosage Form	Solution for subcutaneous injection	Solution for intravenous infusion
How Supplied	Single-dose vials of: • 1400 mg rituximab and 2000 units/mL hyaluronidase per 11.7 mL • 1600 mg rituximab and 2000 units/mL hyaluronidase per 13.4 mL	Single dose vials of: • 100 mg/10 mL (10mg/mL) in a 10 mL • 500 mg/50 mL (50 mg/mL) in a 50 mL
Storage	Store at 2°C to 8°C (36°F to 46°F). Do not freeze. Keep  (b) (4) in the  (b) (4) carton in order to protect from light.	Store at 2°C–8°C (36°F–46°F). Rituxan vials should be protected from direct sunlight. Do not freeze or shake
Preparation/Administration	 (b) (4)	Withdraw the necessary amount of Rituxan and dilute to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute

	(b) (4) Once transferred from the vial into the syringe, the solution of product for subcutaneous injection is (b) (4) for 48 hours at 36°F–46°F (2°C–8°C) and subsequently for 8 hours at 30°C in diffuse daylight. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging. (b) (4)	with other drugs. Discard any unused portion left in the vial. Rituxan solutions for infusion may be stored at 2°C-8°C (36°F-46°F) for 24 hours. Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C-8°C). First Infusion: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Subsequent Infusions: Standard Infusion: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
Likely Care Environment for Dispensing and Use	In-patient hospital clinic setting, primarily will be dispensed from a hospital pharmacy setting.	In-patient hospital clinic setting, primarily will be dispensed from a hospital pharmacy setting.

2 RESULTS

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

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Hematology Products (DHP) concurred with the findings of OPDP’s assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 United States Adopted Names (USAN) Search

There is no USAN stem present in the proprietary name and modifier.^b

^b USAN stem search for root name conducted on 2017 Jan 11; for modifier conducted on 2017 Jan 11.

2.2.2 Components of the Proposed Proprietary Name

The Applicant did not provide a derivation or intended meaning for the proposed name, Rituxan Hycela*** in their submission.

The proposed proprietary name is comprised of multiple words that contain the root name “Rituxan” and modifier “Hycela”. The use of the root name Rituxan and the modifier “Hycela” is evaluated in section 2.2.6.

2.2.3 FDA Name Simulation Studies

Eighty-four (84) practitioners participated in DMEPA’s prescription studies. The responses did not overlap with any currently marketed products nor did the responses sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

2.2.4 Comments from Other Review Disciplines at Initial Review

In response to the OSE, January 03, 2017 e-mail, the Division of Hematology Products (DHP) did not forward any comments or concerns relating to the proposed proprietary name at the initial phase of the review.

2.2.5 Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving *Rituxan* that would be relevant for this review.

Table 2. FAERS Search Strategy	
Search Date	January 19, 2017
Drug Name	*RITUXAN* [product name]
Event (MedDRA Terms)	DMEPA Official PNR Name Confusion Search Terms Event List: Preferred Terms: CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR (DRUG ADMINISTRATION ERROR) DRUG DISPENSING ERROR DRUG PRESCRIBING ERROR INTERCEPTED DRUG DISPENSING ERROR INTERCEPTED DRUG PRESCRIBING ERROR INTERCEPTED MEDICATION ERROR MEDICATION ERROR PRODUCT NAME CONFUSION TRANSCRIPTION MEDICATION ERROR Lower Level Terms: INTERCEPTED PRODUCT SELECTION ERROR INTERCEPTED WRONG DRUG PRODUCT SELECTED INTERCEPTED WRONG DRUG SELECTED

PRODUCT SELECTION ERROR WRONG DEVICE DISPENSED WRONG DRUG ADMINISTERED WRONG DRUG DISPENSED WRONG DRUG PRESCRIBED WRONG DRUG PRODUCT SELECTED WRONG DRUG SELECTED WRONG PRODUCT SELECTED

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

The search yielded 65 cases for review. However, upon analysis, 59 cases were determined to be errors unrelated to name confusion with the proprietary name Rituxan.^c

Following exclusions, six cases were evaluated further. These six cases involve mix-ups between Remicade and Rituxan. Table 4 below provides a summary of the medication errors that involved confusion between Rituxan (rituximab) and Remicade (infliximab).

Table 4: Wrong drug errors between Rituxan (rituximab) and Remicade (infliximab)				
FAERS Case Number	Intended Drug Product	Dispensed Drug Product	Reported Outcome	Reported Root Cause(s)/ Contributing Factors
3392774	Remicade (infliximab)	Rituxan (rituximab)	Order was for Remicade and pharmacy processed and prepared Rituxan. Error was caught by RN and patient did not receive drug.	Proper name similarity between infliximab and rituximab. The pharmacy processed order entry based on proper names.
6213302	Rituxan	Remicade	Order for Rituxan was entered as Remicade in the pharmacy system, and it was not caught by second check by another pharmacist. The technician caught the mistake by comparing label to the order. The patient did not receive	Proprietary name similarities of Rituxan and Remicade.

			drug.	
3802452	Infliximab	Rituximab	Pharmacy technician chose rituximab instead of infliximab. Pharmacist double checked and patient did not receive drug.	Pharmacy personnel indicated that the information on the labels, such as color, strength, and names for both drugs look similar
3915223	Remicade	Rituxan	Pharmacy drug label was for Remicade, but pharmacy technician pulled Rituxan to be mixed. The mistake was caught by pharmacist and did not reach patient.	The root cause was reported as similar dosage.
7388271	Remicade	Rituxan	Patient received Rituxan instead of Remicade on possibly two incidents, and as a result experienced bleeding and “lack of effect” was reported as a result.	The root cause was not reported.
11904359	Remicade	Rituxan	Patient received wrong drug, but no outcome was reported	The root cause was not reported.

Five (5) cases above occurred prior to 2012 and were previously addressed in OSE Review 2012-58.^d At that time, we concluded that there were similarities in both the proper names of rituximab and infliximab as well as proprietary names, Rituxan and Remicade. However, both Rituxan and Remicade have been marketed since 1997 and 1998, respectively, and are widely prescribed products. It was determined that implementation of a proprietary name change would be difficult and ineffective at reducing errors due to the strong name recognition amongst the healthcare community. Therefore, the Institute of Safety Medication (ISMP) published, in collaboration with DMEPA, numerous recommendations for healthcare providers to alert them of the name pair similarities.^e These recommendations included (but not limited to) the use of

^c The following cases were excluded: Incorrect Product Storage (n = 36), Inappropriate Schedule of drug administration (n = 11), Incorrect drug administration rate (n = 1), Incorrect dose administered (n =5), Poor quality drug administered (n =1), Incorrect duration of treatment (n = 1), Drug adverse events (n =1), Unknown medication error (n =3).

^d Defronzo, K. Label and Labeling Review for Rituxan. Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2012 June 19. RCM No.: 2012-58.

^e ISMP References: ISMP Medication Safety Alert! Acute Care Edition. Institute for Safe Medication Practices. April 22, 2004; ISMP Medication Safety Alert! Acute Care Edition. Institute for Safe Medication Practices. February 12, 2004; ISMP

both brand and generic names along with the indication when prescribing these products, instituting independent double-check prior to dispensing and administering either product, and the use of fluorescent stickers in storage bins to alert the staff of the danger for mix-up.

Since our previous review, our current search identified one additional case (Case #11904359) from 2015 regarding wrong drug errors between Remicade and Rituxan.^f This case reported that a patient was intended to receive infliximab, but received rituximab 350 mg (route of administration, and frequency not reported). We evaluated the error report further and determined that there was no evidence of actual name confusion as not enough information was provided in the case with regard to the root cause and contributing factors.

2.2.6 Safety assessment of the root name and modifier

The proposed proprietary name is comprised of two words: the root name ‘Rituxan’ and the modifier ‘Hycela’. The root name, “Rituxan”, is available for intravenous administration in single dose vials of 500 mg/50 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL). The Applicant has developed a co-formulation of rituximab and recombinant human hyaluronidase for subcutaneous injection. The Applicant proposes to use the modifier “Hycela” to differentiate this subcutaneous formulation from the currently marketed intravenous formulation of Rituxan. Differences between the proposed formulation and the current marketed formulation are listed in Table 1 under Section 1.2 of our review.

Given the Applicant’s proposal to use Rituxan as the root name with the addition of a modifier, we considered the following (addressed respectively below): (1) use of the same root name, (2) whether use of a modifier is sufficient to adequately distinguish the products, and (3) whether the proposed modifier (i.e., Hycela) is appropriate.

1. **Use of the same root name:** We performed a FAERS search on January 19, 2017 to identify cases of name confusion with the root name Rituxan. We note cases of name confusion between Rituxan (approved in November 1997) and Remicade (approved in August 1998), specifically between the brand names, Rituxan and Remicade and/or the proper names, rituximab and infliximab (See Section 2.2.5 for additional information). Our search did not identify any new signals. Thus, we do not object to use of the same root name for this product.
2. **Whether use of a modifier is sufficient to adequately distinguish the products:** To inform our evaluation, we reviewed the naming convention used internationally to distinguish the intravenous and subcutaneous Rituxan formulations. Table 5 summarizes the internationally approved (Australia, New Zealand) and marketed (Canada, Singapore, and the European Union (EU)) naming conventions for the Rituxan intravenous and subcutaneous

Medication Safety Alert! Acute Care Edition. Institute for Safe Medication Practices. May 17, 2000; ISMP Medication Safety Alert! Acute Care Edition. Institute for Safe Medication Practices. November 18, 2010; ISMP Medication Safety Alert! Acute Care Edition. Institute for Safe Medication Practices. July 31, 2008; ISMP Medication Safety Alert! Acute Care Edition. Institute for Safe Medication Practices. December 16, 1998.

^f Defronzo, K. Label and Labeling Review for Rituxan. Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2012 June 19. RCM No.: 2012-58.

formulations).[§] Australia, Canada, and New Zealand use the same root name with a modifier to distinguish between the intravenous and subcutaneous formulations, whereas the EU and Singapore do not use a modifier.

Table 5. Summary of Proprietary Names for Rituxan Formulations in Select Countries		
Country	Proprietary Name for Intravenous formulation (strength and vial size)	Proprietary Name for Subcutaneous Formulation (strength presentation)
Australia*	<i>Mabthera</i> (10 mg/mL in 10 mL and 50 mL vials)	<i>Mabthera SC</i> (1400 mg/11.7 mL)
Canada	<i>Rituxan</i> (10 mg/mL in 10 mL and 50 mL vials)	<i>Rituxan SC</i> 1400 mg rituximab (120 mg/ 15 mL)
European Union	<i>Mabthera</i> <i>Labels: Mabthera 100 mg Concentrate for solution for infusion</i> (10 mg/mL in 10 mL vial)	<i>Mabthera</i> <i>Labels: Mabthera 1600 mg solution for subcutaneous injection</i> (1,600 mg/13.4 mL)
	<i>Mabthera</i> <i>Labels: Mabthera 500 mg Concentrate for solution for infusion</i> (10 mg/mL in 50 mL vial)	<i>Mabthera</i> <i>Labels: Mabthera 1400 mg solution for subcutaneous injection</i> (1,400 mg/11.7 mL)
Singapore	<i>Mabthera</i> (10 mg/mL in 10 mL and 50 mL vials)	<i>Mabthera</i> <i>Labels: Mabthera 1400 mg Solution for Subcutaneous Injection</i> (1400 mg/11.7 mL of rituximab)
New Zealand*	<i>Mabthera</i> (10 mg/mL in 10 mL and 50 mL vials)	<i>Mabthera SC</i> (1400 mg/11.7 mL of rituximab)

*Products approved but not yet marketed

Through the FDA/EMA Pharmacovigilance Cluster Teleconference, as well as the FDA 4-Way International Pharmacovigilance Teleconference with the countries listed in Table 5, DMEPA requested that these countries share medication error reports they have received between the two formulations to help inform whether the use of a modifier is sufficient in distinguishing between the two formulations. To date, EMA was the only agency that reported incidence of incorrect route of administration between the two formulations. Other countries indicated they have not received any medication errors that involved confusion between the two formulations.

[§] FDA/EMA Pharmacovigilance Cluster Teleconference. 4 Nov 2016; FDA 4-Way International Pharmacovigilance Teleconference Written Responses. 21 Nov 2016.

Since the approval of the subcutaneous formulation in 2014, the European Medicines Agency (EMA) has received two cases of medication errors involving incorrect route of administration. In these two cases, the subcutaneous rituximab was administered intravenously. In our review of these reports, we note that the root causes were either inconclusive or not provided. We also note that the EU does not use a modifier in the proprietary name to distinguish between the two formulations. Therefore, the use of a modifier may reduce risk of name confusion between the two formulations.

Although the paucity of reports does not provide complete assurance that confusion in the US would not occur due to the propensity for medication errors to be under-reported and because the medication use process and labels and labeling in these countries may have some differences compared to that in the US, this finding provides some reassurance that use of the proposed naming convention may assist in distinguishing the formulations.

- 3. Whether the proposed modifier “Hycela” is appropriate:** We considered whether “Hycela” itself is a suitable modifier from a safety perspective. We found that “Hycela” is not a medical abbreviation and does not contain a USAN stem. We note that the external study conducted by (b) (4) evaluated the risk of proprietary name confusion between the proposed modifier ‘Hycela’ and marketed products. We agree with (b) (4) assessment that the proposed modifier does not appear to present any overt safety concerns from a look-alike or sound-alike perspective.

In summary, we note that there are several differences between the two formulations. The addition of the modifier “Hycela” to the root name, Rituxan, further differentiates the product from the current single-dose vials for intravenous injection. It is not uncommon for modifiers to be used to denote a specific formulation or packaging configuration as part of a product line extension.

However, we also note that omission and oversight of a modifier is cited in literature as a common cause of medication error.^h Postmarketing experience shows that the introduction of product line extensions result in medication errors if the modifier is omitted and the product characteristics are similar or overlap. We also note there is a possibility of wrong dose errors and wrong route of administration if the modifier is omitted or overlooked. Furthermore, the subcutaneous formulation of the drug is more concentrated than the intravenous formulation, and we acknowledge that choosing the wrong drug could potentially result in overdose.

An alternative to using a modifier to distinguish this product from the currently marketed products is to use a different root name. However, marketing the new product under a unique proprietary name also carries a risk of medication errors, such as therapeutic duplication and overdoses. These errors may have greater associated safety risks than the omission or oversight of the modifier as discussed above.

Therefore, for the aforementioned reasons, DMEPA finds that the proprietary name “Rituxan Hycela”, although not free from the risk of error, offers a safer approach to naming this product. In addition, the residual risk of confusion between the intravenous and subcutaneous formulations of the product may be mitigated through labels and labeling intervention.

^h Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

2.2.8 Communication of DMEPA's Analysis at Midpoint of Review

DMEPA communicated our findings to the Division of Hematology Products (DHP) via e-mail on March 8, 2017. At that time we also requested additional information or concerns that could inform our review. Per e-mail correspondence from the DHP on March 8, 2017, they stated no additional concerns with the proposed proprietary name, Rituxan Hycela.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Neil Vora, OSE project manager, at 240-402-4845

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Rituxan Hycela, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your December 13, 2016 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. *USAN Stems* (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page>)

USAN Stems List contains all the recognized USAN stems.

3. *Electronic Drug Registration and Listing System (eDRLS) database*

The electronic Drug Registration and Listing System (eDRLS) was established to support the FDA's Center for Drug Evaluation and Research (CDER) goal to establish a common Structured Product Labeling (SPL) repository for all facilities that manufacture regulated drugs. The system is a reliable, up-to-date inventory of FDA-regulated, drugs and establishments that produce drugs and their associated information.

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.^j

***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, CernerRxNorm, and names in the review pipeline using a 50% 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 $\geq 70\%$.
- Moderately similar pair: combined match percentage score $\geq 55\%$ to $\leq 69\%$.
- Low similarity: combined match percentage score $\leq 54\%$.

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

Three 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 or verbal pronunciation of the drug name. 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 orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail.

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

The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

- c. 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. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA’s final decision on the proposed 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 $\geq 70\%$).

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.			
<u>Orthographic Checklist</u>		<u>Phonetic Checklist</u>	
Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more</i>	Y/N	Do the names have different syllabic stresses?

	<i>letters.</i>		
Y/N	Considering variations in scripting of some letters (such as <i>z</i> and <i>f</i>), 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 as 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 $\geq 55\%$ to $\leq 69\%$).

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:

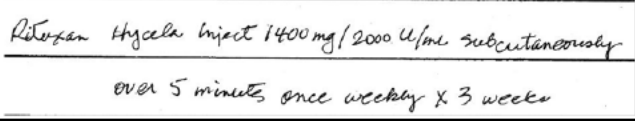
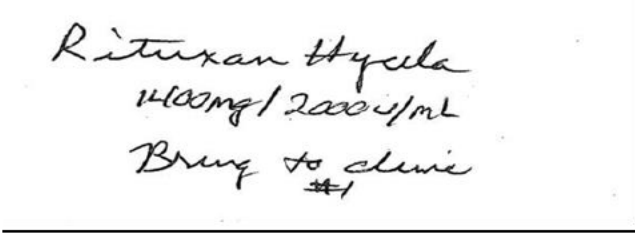
	• Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • 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 with overlapping or similar strengths or doses.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

Appendix B: Prescription Simulation Samples and Results

Figure 1. Rituxan Hycela Study (Conducted on January 24, 2017)

Handwritten Medication Order/Prescription	Verbal Prescription
<u>Medication Order:</u>  Rituxan Hycela Injct 1400 mg/2000 U/ml subcutaneously over 5 minutes once weekly x 3 weeks	Rituxan Hycela 1400 mg/2000 U/mL Bring to clinic 1 Vial
<u>Outpatient Prescription:</u>  Rituxan Hycela 1400mg/2000U/ml Bring to clinic #1	

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

297 People Received Study

84 People Responded

Study Name: Rituxan Hycela

Total	31	19	34	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
PACK	1	0	0	1
RATUXAN HYCELA	0	0	1	1
RITAXAN HYCELA	0	0	2	2
RITOXAN HYCELA	0	0	6	6
RITREXAN HYCELA	1	0	0	1
RITUXAN	1	0	0	1
RITUXAN HIGH SELLER	0	1	0	1
RITUXAN HISTELLA	0	1	0	1
RITUXAN HYAKA	1	0	0	1
RITUXAN HYALA	4	0	0	4
RITUXAN HYCELA	11	1	23	35
RITUXAN HYCELA INJECT	0	0	1	1
RITUXAN HYCELLA	0	2	0	2
RITUXAN HYCELSA	0	0	1	1
RITUXAN HYCILA	5	0	0	5
RITUXAN HYCLA	1	0	0	1
RITUXAN HYELA	1	0	0	1
RITUXAN HYUCILA	1	0	0	1
RITUXAN HYULA	3	0	0	3

RITUXAN XXX	0	1	0	1
RITUXIN HIFELLA	0	1	0	1
RITUXIN HIGHCELLA	0	1	0	1
RITUXIN HYCELA	0	1	0	1
RITUXIN HYCELLA	0	2	0	2
RITUXIN HYSELA	0	1	0	1
RITUXINHISELLA	0	1	0	1
RITUZAN HYCILA	1	0	0	1
RYTAXIN HYTELA	0	1	0	1
RYTUSSIN HYCELLA	0	1	0	1
RYTUXAN HICELLA	0	1	0	1
RYTUXIB HYSILLA	0	1	0	1
RYTUXIN HYSELLA	0	1	0	1
RYTUXIN HYTELA	0	1	0	1

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/s/

LEEZA RAHIMI
03/09/2017

HINA S MEHTA
03/09/2017

MISHALE P MISTRY
03/10/2017

PROPRIETARY NAME 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: 07 November 2016

Application Type and Number: BLA 761064

Product Name and Strength: (b) (4) (rituximab/hyaluronidase) Injection
1400 mg and 2000 U/mL per 11.7 mL, 1600 mg and
2000 U/mL per 13.4 mL

Total Product Strength: (120 mg and 2000 U/mL)/mL, (b) (4)
(b) (4)

Product Type: Multi-Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Genentech

Panorama #: 2016-10042968

DMEPA Primary Reviewer: Leeza Rahimi, Pharm.D.

DMEPA Acting Team Leader: Hina Mehta, Pharm.D.

DMEPA Deputy Director: Lubna Merchant, M.S, Pharm.D.

DMEPA Director: Todd Bridges, RPh

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